NCGC National Clinical Guideline Centre

Pharmacological Update of Clinical Guideline 20

The Epilepsies

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

See page 4 for update information for this guideline

Final

Methods, evidence and recommendations

January 2012

Commissioned by the National Institute for Health and Clinical Excellence

Preface

Dr Richard Roberts

Consultant Neurologist, Ninewells Hospital, Dundee

Chairman, SIGN 70 Diagnosis and management of epilepsy in adults (2003)

The inadequacies that have existed in the services, care and treatment for people with epilepsy are well recognised. Important issues include misdiagnosis, inappropriate or inadequate treatment, sudden unexpected death that might have been prevented, advice about pregnancy and contraception and management of status epilepticus. Service provision for people with epilepsy has been patchy and sometimes poor both in primary and secondary care. This is now changing. The new General Medical Services (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.

Dr Nick Kosky

Consultant Psychiatrist, Prison Mental Health Inreach Team and Medical Director, Dorset Community Health Services

Chairman, The epilepsies guideline 2012

The first NICE guideline on the management of epilepsy in children and adults was published in 2004.

Update 2012

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published 2004

The guideline highlighted the inadequacies that existed in the services, care and treatment for people with epilepsy, and made great progress in addressing relevant important issues - misdiagnosis, inappropriate or inadequate treatment, sudden unexpected death that might have been prevented, advice about pregnancy and contraception and management of status epilepticus.

Revisiting this guideline is timely. The NHS is facing major financial challenges, and it is vital that a spotlight is kept on the need to further develop the still variable services for people with epilepsy. The place of newly licensed drugs for epilepsy also needs careful consideration.

The updated guideline reminds the reader of the need for properly resourced services, offering appropriate levels of expertise, which allow timely access to assessment and treatment for people with epilepsy. The primary scope of the guidelines was to consider the role of antiepileptic drugs, especially given the impact of important, real-world studies such as SANAD. The role of established and newly licensed drugs has been considered using novel statistical methods allowing comparison of cost effectiveness – a process that has been much aided, as always, by a robust stakeholder review process.

People with epilepsy remain at the centre of this guideline, and the need for services to consider the needs of each individual, to not discriminate in provision and to work in partnership with people with epilepsy and their carers is underlined.

Attention has been paid to ensure that the recommendations are written in clear language and are accessible, and, we hope, useful to all. Supporting the written version is an online care pathway, and quality standards are soon to be published. We remain committed to the care of people with epilepsy and commend these guidelines to you in that light.

Update 2012

Foreword

Dr Mayur Lakhani

Chairman-Elect, Royal College of General Practitioners until 2006

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.

Update information

October 2019: Because of a risk of abuse and dependence, gabapentin and pregabalin are controlled under the Misuse of Drugs Act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3 (as of 1 April 2019). Tables have been amended and a footnote has been added to this guideline to reflect this change.

April 2018: Footnotes and cautions in the guideline have been added and amended to link to the MHRA's latest advice and resources on sodium valproate. Medicines containing valproate taken in pregnancy can cause malformations in 11% of babies and developmental disorders in 30 -40% of children after birth. Valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless alternative treatments are not suitable and unless the terms of the pregnancy prevention programme are met. This programme includes: assessment of patients for the potential of becoming pregnant; pregnancy tests; counselling patients about the risks of valproate treatment; explaining the need for effective contraception throughout treatment; regular (at least annual) reviews of treatment by a specialist, and completion of a risk acknowledgement form. In pregnancy, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation. See the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy.

Appendices A and B (details of internal/external staff and committee members) were removed as this information is now available elsewhere on the NICE website.

February 2016: The Medicines and Healthcare Products Regulatory Agency (MHRA) has produced a toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy. Healthcare professionals are advised to use the NICE guideline in conjunction with the latest MHRA advice and resources. Footnotes and cautions in the guideline have also been added and amended to link to the MHRA's latest advice and resources.

January 2015: The Medicines and Healthcare Products Regulatory Agency (MHRA) has strengthened its warnings on the use of valproate in women of childbearing potential. We are assessing the impact of this on the guideline. In the meantime, healthcare professionals are advised to use the guideline in conjunction with the latest MHRA advice.

November 2013: A footnote has been added to recommendation 1.9.1.4 highlighting new advice issued by the MHRA about oral anti-epileptic drugs (AEDs).

These changes can be seen in the short version of the guideline at:
http://www.nice.org.uk/guidance/CG137

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Update 2012

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2004

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2012

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1 Introduction

1.1 Definition of epilepsy

2004

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 [1].

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

2004

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.[2] The classification of the epilepsies is controversial and has tended to focus on both the clinical presentation (type of epileptic seizure) and on the underlying neurological disorder (epilepsies and epilepsy syndromes).[3]

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.[4] 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 with epilepsy have convulsive seizures, of which two thirds have focal epilepsies and secondarily generalised seizures and the other third will have generalised tonic-clonic seizures.[1,6,7] 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]

2012

Since 2004, discussion with regard to the classification of the epilepsies has continued. With advances in technology, particularly imaging and genetics, some of the older termininology eg idiopathic/symptomatic/cryptogenic, has become redundant in general use. Furthermore, although seizures may be focal or generalised in onset, such terminology cannot be applied to syndromes. The terms partial, complex and simple are also replaced simply by focal.

Ensuring an accurate diagnosis is important for planning management. Although the primary aim is to diagnose a recognisable electroclinical syndrome, it is recognised this may not be possible in a not insignificant number of individuals. The exact syndrome diagnosis may not be readily apparent at presentation. Moreover, in some, the cause may be of equal importance. A more descriptive approach has been recommended, retaining the electroclinical syndromes where possible but where underlying aetiology is taken into account [12]. This has implications for treatment in an increasing number of situations.

Update 2012

1.3 Epidemiology

2004

The epilepsies comprise the most common serious neurological disorders in the UK. It affects between 260,000 and 416,000 people in England and Wales (Appendix G).[13]

The incidence of epilepsy is about 50 per 100,000 per annum.[14] 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.[15,16] 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).[17] 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.[18]

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 or learning difficulties. [19]

2012

Analysis of data from the Quality and Outcomes Framework (QOF) epilepsy diagnostic codes suggest a prevalence of diagnosed epilepsy in people aged 18 and over of 1.15%. The use of data from administrative databases such as the QOF, however, which incorporate non-validated epilepsy diagnostic codes for the estimation of prevalence rates is fraught with difficulty and there is a tendency for such databases to overestimate prevalence. There are no direct estimates of the epilepsy prevalence for England. Some existing data using validated methods, suggest the prevalence

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to be between 0.7 to 0.8% for the whole population [*] [†]Based on a population in England of 51,810,000 in 2009 (<http://www.statistics.gov.uk/downloads/theme_population/mid-09-uk-eng-wales-scot-northern-ireland-24-06-10.zip) this would suggest there are between 362,000 and 415,000 people with epilepsy in England. In addition, there will be individuals, estimated to be a further 5-30%, so amounting to up to another 124,500, who have been diagnosed with epilepsy, but in whom the diagnosis is incorrect [‡].The rate of learning disability in the epilepsy population remains high; in particular children with early onset epilepsy are highly likely to experience neurodevelopmental compromise [20]. Even in those with later onset, numbers with any degree of learning disability are thought to be underestimated. The prevalence of behaviour disorder in children with epilepsy also remains high. The British child and adolescent mental health survey, questioning 10,438 children in the UK age 5-15 years, found a prevalence of behaviour disorder in children with 'pure' epilepsy to be up to three times that of another chronic disorder (diabetes, 10.2%) or the general population (9.3%) and in 'epilepsy plus', almost six times (56%) [21]. Both may be compounded by medication and must therefore be taken into consideration when discussing medication to use.

An increasing population is the elderly, in whom the incidence of new onset epilepsy is increasing, although the possibility of misdiagnosis also remains high [22]. Special consideration needs to be given when prescribing any medication within this population, not least because of drug interaction and pharmacokinetic issues, and this similarly applies to antiepileptic medication. Increasing information is also being gathered on the effect of antiepileptic drugs taken by a mother on the unborn child; further data have to be accumulated to ensure accurate information on treatment and its possible effects are given to a woman prior to conception so she is able to make choices [23].

1.4 Cost of epilepsy

2004

The medical cost to the NHS in 1992/1993 of newly diagnosed epilepsy in the first year of diagnosis was calculated as £18 million and the total annual cost of established epilepsy estimated at £2 billion (direct and indirect costs), over 69% of which was due to indirect costs (unemployment and excess mortality).[24]

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 literature[25] 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.[25]

[*] MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and prevalence of neurological disorders in a prospective community based study in the United Kingdom. Brain 2000; 123:665-676

[†] Purcell B, Gaitatzis A, Sander JW, Majeed A. Epilepsy prevalence and prescribing patterns in England and Wales. Health Statistics 2002; 15: 23-31.

[‡] Chowdhury FA, Nashef L, Elwes RD. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. Eur J Neurol. 2008 Oct;15(10):1034-42.

2012

Since 2004, a further five AEDs have become licensed for use in the UK for the treatment of epilepsy. A more recent cost analysis estimated the total cost of epilepsy in Europe in 2004 was 15.5 billion Euros; the cost of antiepileptic drug use being €400,000 [26]. Economic cost however is only one aspect to be considered when discussing the cost of epilepsy to the individual. Lost employment, hospital visits and overall life disruption/quality of life need to be carefully considered. Studies reviewing quality of life of individuals with epilepsy highlight important determinants to be seizure freedom and medication side effects amongst others[27]. Seizure freedom should be strived for in each individual who presents with epilepsy, although not at the expense of excessive side effects. Choices of anti-epileptic medication therefore have to measured and tailored to the individual, informed by data available from the existing evidence base.

Update 2012

1.5 Health Services for people with epilepsy

2004

Since 1953 six major reports[11,18,28-31] have made recommendations to improve services for people with epilepsy in the UK, but these services remain patchy and fragmented.[13] The Department of Health has recently published an action plan[32] to improve services for people with epilepsy in response to the National Sentinel Clinical Audit (SUDEP report).[18]

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.

2012

Since 2004, the clinical guideline recommendations have provided a framework by which epilepsy services can be improved. However services remain patchy; a further report in 2008 by the All Party Parliamentary Group on epilepsy (wasted money, wasted lives) recognised that in some areas many of the recommendations as published in 2004 had not been implemented, and that an early review was required as to the progress of implementation of the NICE guidelines in England & Wales. Furthermore, the wider need for training was also recognised. Currently HQIP in collaboration with the British Paediatric Neurology Association and the Royal College of Paediatrics and Child Health have initiated a national audit of childrens services (Epilepsy12), measured against various performance measures as defined by the 2004 guideline, due to publish in 2014.

Update 2012

1.5.1 Primary care

2004

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 care plans; triggers for referral were sometimes missed, and there were failures of communication between primary and secondary care.[18]

2012

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

Update 2012

1.5.2 Secondary care

2004

The majority of people with epilepsy receive most of their initial care in secondary care and those whose seizures are not well controlled continue to receive ongoing care in secondary care. The SUDEP report identified deficiencies in care provided to both adults and children in secondary care.[18]

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.

2012

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

Update 2012

1.6 The SANAD trial

The SANAD trial was a pragmatic, randomised, unblinded, parallel group clinical trial comprising two arms (one comparing new AEDs with carbamazepine and the other comparing newer AEDs with sodium valproate). It was commissioned and sponsored by the NHS R&D Health Technology Assessment Programme, but also supported by the pharmaceutical companies with AEDs included in the study, who contributed approximately 20% of the total costs of the study. It received appropriate multicentre and local ethics and research committee approvals, and patients gave informed consent to inclusion and to long-term follow-up. It also achieved the involvement of a large number of

Update 2012

physicians for a long-term collaboration. The methodology of the study involved physicians deciding on diagnosis of an individual with epilepsy, and whether their drug of choice would be sodium valproate or carbamazepine. If the choice was sodium valproate, individuals were randomised to receive sodium valproate, lamotigine or topiramate (Arm A); if the choice was carbamazepine then the individual would be randomised to carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate. (Arm B).

A total of 1721 patients were recruited to Arm A and 716 to Arm B. Arm A recruited 88% of patients with symptomatic or cryptogenic partial epilepsies and 10% with unclassified epilepsy. Arm B recruited 63% of patients with idiopathic generalised epilepsies and 25% with unclassified epilepsy.

The study provides evidence that lamotrigine may be a clinical and cost-effective alternative to the existing standard drug treatment for focal seizures, carbamazepine. Some 88% of patients in Arm A were diagnosed as having focal seizures, so conclusions are applicable to patients with these epilepsy syndromes. For patients in Arm B with idiopathic generalised epilepsies or difficult to classify epilepsy, sodium valproate remained the clinically most effective drug, although topiramate may be a cost-effective alternative for some patients.

The authors of SANAD challenge previous RCTs on AED monotherapy efficacy that "fail to inform clinical practice of policy", and despite some of the perceived methodological limitations it is a very important trial of first AED therapy.

The results suggest that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in focal epilepsies. It was therefore considered necessary to review new evidence regarding anti-epileptic drugs within an update of the NICE clinical guideline.

For further details on the quality assessment of the SANAD trial, please refer to the relevant seizure type/syndrome chapters.

1.7 Guideline aims

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'.[33]

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

1.8 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.

1.9 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).

1.10 Structure of guideline documentation

2004

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).

2012

The guideline is divided into sections which cover in detail specific topics relating to the treatment and management of people with epilepsy. For each topic the layout is similar.

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

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

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

evidence was retrieved. These evidence statements provide the basis on which the guideline development group made their recommendations.

The recommendations are presented in both the executive summary and in the last section in each evidence review. For the purposes of the guideline update, the [2004] recommendations will be in a blue shaded box at the start of a new section, whilst the new recommendations [2012] and [New 2012] will be at the end of each section with the relevant evidence to recommendations.

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

Labelling of recommendations

- New recommendations are defined as either an additional area for the guideline or changed because of an updated evidence review. New recommendations are labelled by adding [NEW 2012] to the end of the recommendation.
- Unchanged recommendations where the evidence has been reviewed for the 2012 update are labelled as [2012]. These recommendations could be reworded to match new-style recommendations but the developers checked with the GDG that rewording hasn't changed the meaning.
- Unchanged recommendations from 2004, where the evidence has not been formally reviewed for the 2011 update, are labelled as [2004].
- Where evidence has not been reviewed, but there have been minor changes in 2012 to the wording of a 2004 recommendation that do not affect the meaning, for specific reasons such as in terminology or availability of drugs, these are labelled as [2004, amended 2012].

Deleted recommendations from the 2004 guideline can be viewed in Appendix X

1.11 Guideline limitations

The guideline documentation and recommendations are subject to various limitations. The National Institute for Health and 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.

1.12 Plans for updating the guideline

2004

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.

2012

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

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

2 Methods

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the National Institute for Health and 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 2004 edition of this guideline was developed by the National Collaborating Centre for Primary Care (NCC-PC). The NCC-PC was based at the Royal College of General Practitioners (RCGP), and involved the following partners: Royal College of General Practitioners, Royal Pharmaceutical Society of Great Britain, Community Practitioners and Health Visitors Association, and the Clinical Governance Research and Development Unit (CGRDU), Division of General Practice and Primary Healthcare, Department of Health Sciences, University of Leicester. The Collaborating Centre was set up in 2000, to undertake commissions from the National Institute for Clinical Excellence to develop clinical guidelines for the National Health Service in England and Wales.

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

2.2.2 The National Clinical Guidelines Centre

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

2.2.3 The methodology team

2004

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

2012

The methodology team was led by the Guidelines Operations Director of the National Clinical Guidelines Centre (NCGC), and comprised: a senior research fellow who acted also as project manager, two systematic reviewers, one health economist and two information scientists. Advice and guidance was also sought from the clinical advisor (Professor Helen Cross), the appointed Chair of the Guidelines Development Group (Dr Nick Kosky), and members and co-optees of the GDG.

Update 2012

2.2.4 The Guideline Development Group

2004

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.

2012

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

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

The professional representatives on the group were chosen according to a set process. The NCC-PC project team decided on the necessary professional representation required for the GDG, based on the scope of the guideline. Professional registered stakeholder organisations were written to to notify them of the advertisement and recruitment process. Once all of the applications were received, the NCC-PC Clinical Director, chairman and the project lead selected the individual members, on the basis of their CVs, supporting statements, and against a selection criteria adapted from the person specification and job description.

For the patient members, the PPIP at NICE submitted the received applications, from which the NCC-PC Clinical Director, chairman and the project lead chose two as patient members based on the aim (as with the professional healthcare applicants) of including as wide a range as possible of expertise, experience, and geographic representation from across England and Wales.

In accordance with guidance from NICE, all GDG members and the chair declared in writing interests that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the

healthcare industry and these were made available in the public domain. Details of these can be seen in Appendix U. Declaration of interests were updated at the start of each GDG meeting. A record of updated declarations of interest was recorded in the NCGC's database and minutes of each meeting were produced. The minutes of the GDG meetings were published on the NICE website within 10 weeks of being agreed by the GDG.

Update 2012

2.3 Developing key clinical questions (KCQs)

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

The KCQs were developed by the GDG, with input as appropriate from co-optees and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis [34].

2004

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.

2012

A total of 22 **new** KCQs were identified;

- Seventeen key clinical questions focused on the effectiveness and cost-effectiveness of AEDs and had common stems for children and adults;
- Three key clinical questions specifically addressed children; two of these key clinical questions adressed the effectiveness and cost effectiveness of AEDs in treating children with childhood absence epilepsy and children with infantile spasms. The third key clinical question assessed the clinical effectiveness and cost-effectiveness of treating children with the ketogenic diet;
- One key clinical question focused on the clinical effectiveness, cost effectiveness of AEDs and the safety of their use in pregnant women and women currently breastfeeding;
- One key clinical question addressed which AEDs are the most well tolerated for older people, who, for the purposes of this guideline, were defined as those aged 65 years and over.

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

2.4 Identifying the evidence

2.4.1 Literature search strategies

2004

The aim of the literature review was 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.[35] 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.

2012

The aim of the literature search was to update the relevant evidence from the 2004 guideline and to identify new 'evidence within the published literature,' to answer the clinical review questions as per The NICE Guidelines Manual (2009) [36]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Non-English studies were not reviewed and were therefore excluded from searches. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, Medline, Embase, Cinahl and The Cochrane Library. Initial searches for each section were performed when the

literature was needed for the review. Each search was updated 3 months and 6 weeks before the end of guideline development period. No papers indexed in the databases after this date were considered.

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

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

- Constituent websites of the Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

2.4.2 Health economics

2004

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.

2012

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

The search strategies for health economics are included in Appendix J. All searches were updated on prior to consultation. No papers published indexed in the databases after this date were considered.

2.5 Reviewing and grading the evidence

2.5.1 Methods for 2004 Guideline

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

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

The papers chosen for inclusion were obtained and assessed for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differed accoring to study type and were based on the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN).[37] Critical appraisal was carried out by the systematic reviewer. To minimise bias in the assessment, a sample of papers was independently appraised by the project lead. Further appraisal was provided by the GDG members at the relevant GDG meeting.

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

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

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

For each clinical question, the highest level of evidence was selected. If a systematic review, meta-analysis or RCT existed in relation to an EBQ, studies of a weaker design were ignored.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables (Appendix F).

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

2.5.2 Methods for 2012 Guideline

2.5.2.1 Quality assessement for intervention studies

For each clinical question the highest level of evidence was sought. We included only randomised controlled trials as they are considered the most robust type of a study design that could produce an unbiased estimate of the intervention effects. Where an appropriate randomised (double blinded, single blinded or unblinded) controlled trial was identified, we did not search for studies of a weaker design. The quality assessment criteria as listed in the NICE Guidelines Manual 2009 [36] were used to assess systematic reviews, meta-analysis, and randomised controlled trials.

For randomised controlled trials, the main criteria considered were:

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

2.5.2.2 GRADE (Grading of Recommendations Assessment, Development and Evaluation)

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

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

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

The GRADE toolbox is currently designed only for randomised controlled trials and observational studies.

2.6 Methods of combining studies (2012)

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

Where appropriate, sensitivity analyses based on the quality of studies were carried out to explore the impact of including crossover and unblinded studies, and their findings informed the evidence review and GDG considerations of the evidence.

Time to event data were summarized using methods of survival analysis. The intervention effect was expressed as a hazard ratio (HR) following the proportional hazards assumption (an assumption that hazard ratio is constant across the follow-up period). Where appropriate, hazard ratios and variances for time to event outcomes were pooled according to the inverse of variance method with the use of Review Manager software.

2.7 Protocol for guideline evidence reviews for the partial update (2012)

The 2012 version of the guideline was a partial update of the 2004 version and centred on an update of the pharmacological management (also applicable to people with learning disabilities, older people and pregnant women) and the section on ketogenic diet. The evidence reviews conducted as part of the guideline development followed the agreed reviewing protocol outlined below:

Types of studies

Double-blinded, single-blinded and unblinded, parallel and cross-over randomised controlled trials (RCTs were included in the evidence reviews conducted for the partial update (2011). Cross-over trials that did not report the placebo arm data were excluded.

We included randomised controlled trials, as they are considered the most robust type of a study design that could produce an unbiased estimate of the intervention effects. However, there are some limitations of this approach that need to be highlighted; regulatory trials in epilepsy usually have only a limited period of follow-up , and can sometimes use dosing regimens that are not entirely in line with subsequent clinical practice. Therefore, the study dosages have always been checked for accordance with the therapeutic ranges listed in the BNF.

Study designs other than RCT were sought when no RCT data was available for certain clinical questions deemed to be high priority by the GDG (e.g evidence review on teratogenicity of AEDs in pregnancy). However, as time was limited, it was not possible to do this for all questions where there was no RCT evidence. For example we did not search non-RCT evidence for the efficacy of AEDs in CSWS, Landau-Kleffner syndrome or myoclonic-astatic epilepsy (MAE) even though no RCT evidence had been found.

One high quality individual patient data network meta-analysis [38] was identified during stakeholder consultation. The GDG agreed that this was a high quality study that should be incorporated into the evidence reivew. The individual patient data for 6418 patients from 20 randomised controlled trials was incorporated into monotherapy for newly diagnosed focal and generalised tonic clonic seizures

evidence reviews to complement the findings of the pair-wise meta-analyses and assist the GDG in terms of their decision-making and recommendation development.

We included non-inferiority, equivalence and superiority studies but did not include single arm non-comparative trials. Dose-response trials without a comparative drug or placebo arm were therefore excluded. We did not include response-selected trials whereby only participants who responded to a drug were included in the trial. The results of these studies would have been biased towards the drug as the participant had already responded to it.

For the comparisons for which blinded trials were not available, the GDG downgraded the level of quality due to the higher risk of bias. However, the difficulty of blinding in these trials and the trade off between possible higher bias in unblinded studies against the wider clinical applicability was noted by the GDG.

Cross over trials were included in the meta-analysis and analysed as parallel trials by treating the results from the first period as if they came from one group of patients and results from the second period as if they came from a different group of patients. Although this approach can increase a unit-of-analysis error, it is considered to be a conservative analysis, in that studies are under-weighted rather that over weighted.

Originally, we aimed to take into consideration the paired design of the cross over trials by estimating the appropriate standard errors for two period cross over trials using a method developed by Becker and Balagtas (as reported in the paper by Elbourne et al, 2002[39]). However, no cross over trial included in the evidence reviews provided the data for the estimation of standard errors and due to time constraints, authors were not contacted regarding the individual participant data of the trials. Therefore, the decision was made to analyze cross over trials as if they were parallel studies.

The Cochrane Reviews listed in the Cochrane library which included drugs for broad populations; drugs for specific seizure types ; and specific syndromes were cross-referenced as quality assurance for the search strategies. For further details on these reviews, please refer to http://www.thecochranelibrary.com/view/0/index.html.

Types of participants

Adults and children were included in the evidence reviews. They were analysed and presented in separate evidence reviews unless the data were not stratified in the trials. For the purposes of the guideline recommendations, children were defined in this guideline as ranging from 28 days to 11 years, young people from 12 to 17 years and adults 18 years and older. For the purposes of the analyses, children ranged from 28 days to 17 years, and adults were defined as aged 18 years and older.

The mean age at baseline in each trial arm was used to determine whether a trial would be included in adult or children evidence review. However, recent EMA decisions regarding licensing of AEDS for use in children indicate that for 'focal epilepsies especially cryptogenic and symptomatic, and idiopathic generalised epilepsies, with absences, myoclonic and/or generalised convulsive seizures, the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established.' As a result of this, and with the agreement of the GDG, data for adults and children was combined in refractory focal seizures.

The GDG asserted that structuring the guideline according to epilepsy seizure type or syndrome would be the most useful to practicing clinicians, and most clinically meaningful. It would also allow for the potential for a given AED to be therapeutic for a specific seizure type (or syndrome or population) to be established. In clinical practice, choice of AED at presentation should be by epilepsy

syndrome where possible, but where unclear, seizure type (or most likely epilepsy syndrome by age of onset) provides a guide to treatment in the first instance.

However, many studies do not specify a particular epilepsy seizure type or syndrome in their inclusion criteria, nor do they stratify their results according to these seizure types and syndromes. This "contamination" of the seizure type of interest meant that many of the patients could not be categorised. This was particularly common in newly diagnosed conditions as the seizure type may not have been established. Consequently, the GDG decided to use a "contamination" cut-off point for the minimum proportion of trial participants with the relevant seizure type that would be allowed within a given study. This cut off point was set by the GDG to be a minimum of 80% for focal seizures and a minimum of 60% for generalised seizures (both primary generalised tonic-clonic seizures and idiopathic generalised epilepsy) at baseline. This was used for the clinical questions on the effectiveness of AEDs in treating focal seizures with or without secondary generalisation; generalised tonic-clonic seizures; and idiopathic generalised epilepsy. The GDG accepted that these thresholds, whilst arbitrary, reflect the degree of imprecision in clinical practice and likely inclusion error. Studies were excluded where the proportion of patients with the seizure type of interest was less than the cut off point for both focal and primary generalised seizures.

Types of interventions

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

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

Duration of studies

No particular time duration was specified for our inclusion criteria.

Posology

The doses given within the studies were checked according to the usual doses ranges specified in the British National Formulary, and the maximum and minimum doses specified in the summary of product characteristics (SPC). Any trial dose outside these ranges was not included in the meta-analysis. If a study assessed different doses (e.g. more than two study arms) within the usual therapeutic range, then these were amalgamated for the purposes of the meta-analysis. The GDG thought it important to look for AEDs and the doses which were appropriate in a clinical setting rather than just in a trial setting. Most of the exclusions were particular arms of the trial where the dosage was outside of the advised range. We included the other arms of the trial (if within range) in the meta-analyses. Five trial arms were completely excluded due to dosage.

Types of outcome measures and definitions

We extracted data on the following outcomes from the trials:

- The proportion of seizure-free participants: participants seizure free on an intention to treat (ITT) analysis over a defined period during maintenance.
- The proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders): those experiencing a >50% reduction in seizures over a defined end of maintenance period compared to baseline on ITT analysis.
- The proportion of participants having treatment withdrawn: the proportion of participants on ITT analysis who were withdrawn from the study prior to the predefined time period of maintenance treatment.
- Time to exit/withdrawal of allocated treatment (retention time): Period of time from randomization to exit from treatment (withdrawal from treatment), either for lack of efficacy seizures or adverse events.
- Time to first seizure: Time from randomisation to first seizure
- Time to 12 month remission: Time from randomisation to the achievement of a 12 month period without seizures
- Incidence of adverse events (10% or above): incidence of reported adverse event at any time during study period, as reported within the study as a proportion of the total randomised, (>10% taken as significant for reporting).
- Any outcomes relating to cognitive effects.
- Any outcomes relating to quality of life.

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

The outcomes chosen were the same as those reported in the HTAs "Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation"[40], "The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy" and the previous guideline and these reflected many of the outcomes within various epilepsy Cochrane reviews. For the primary outcome measures of studies reviewing efficacy of medication in the treatment of epilepsy, the GDG chose seizure freedom as the most important outcome measure, (most reliably assessed as time to 12 months remission), and thereafter, for adjunctive therapy, those with more than 50% reduction of seizures from baseline. The aim of all antiepileptic treatment is for the individual to achieve seizure freedom with minimal if any side effects. When initial drugs have failed and adjunctive treatment is used seizure reduction is likely to be the aim. Seizure freedom was defined as participants being seizure free on an ITT analysis over a predefined period during maintenance. More than 50% reduction in seizure frequency was defined as those experiencing a >50% reduction in seizures over a defined end of maintenance period compared to baseline, on an intention to treat analysis.

The GDG recognised that many of the studies were performed over a relatively short period of time, and that the majority used these measures as the primary outcome variables. The GDG also agreed not to restrict the time period for measurement of the proportion of seizure-free participants, proportion of participants experiencing at least a 50% reduction in seizure frequency, and proportion of participants having treatment withdrawn. The most ideal measure of effect would appear to be time to exit from study, whether due to lack of efficacy or adverse events as a measure of retention on the medication. Limited studies appear to have reported these data. Where available this was utilised. The GDG recognised that the most reliable measure of efficacy (seizure freedom) and retention was likely to be time to 12 months remission.

Most included trials reported incidence of a range of adverse events. The GDG agreed on using an arbitrary cut-off of point of above an incidence of 10% to prioritise the list of adverse events

retrieved from the trials, as they considered that 10% was a well established proportion for an adverse event.

Type of analysis

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

It is important to note that ITT analyses tend to bias the results towards no difference. They may not be the most appropriate analysis when attempting to establish equivalence or non-inferiority of a treatment. Because of this a sensitivity analysis was perfomed where there was differential drop-out greater than 20% to assess whether this affected the recommendation. This sensitivity analysis was not run where data was available from the Individual Patient Data (IPD) network meta-analyses as it was felt that this had already been taken into account by the IPD. We have used a conservative approach to analyse the data, and therefore acknowledge that the effect may be smaller than in reality.

Use of unpublished data in the guideline

A large multicentre trial (SANAD) has been published, since the publication of the 2004 guideline as well as the newer AED health technology appraisals, which evaluated the efficacy of AEDs against standard treatment, dependent on whether carbamazepine or sodium valproate would be drug of choice (Marson 2007)[41]. Arm B of the published SANAD document collected and reported as baseline data syndrome data but did not provide analyses stratified per syndromes or certain seizure types and therefore the data did not follow the same stratification that was used in the guideline evidence reviews. Because of the relative importance of this trial, we contacted the lead author to determine whether further subgroup analyses according to the syndromes, seizure types, and outcomes of interest to the guideline evidence reviews had been conducted. Unpublished data on the following subgroups was provided by the authors: juvenile myoclonic epilepsy, absence seizures and epilepsy with generalised tonic clonic seizures only. The outcomes included time to 12 month remission, time to treatment failure, time to first seizure and incidence of adverse events. When unpublished SANAD data has been used within the analyses, this has been referenced as “work in progress” in the relevant GRADE profile tables. It is also included within the IPD network meta-analysis [38].

2.8 Grading of quality of evidence for outcomes (2012)

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

1. The evidence for all outcomes start with a HIGH quality rating as only RCTs were considered.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below.
3. The downgrade marks are then summed. Each quality element being considered as having “serious” or “very serious” risk of bias were rated down -1 or -2 points respectively. All studies

started as HIGH and the quality became MODERATE, LOW or VERY LOW when 1, 2 or 3 points were deducted respectively.

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

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

Inconsistency

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

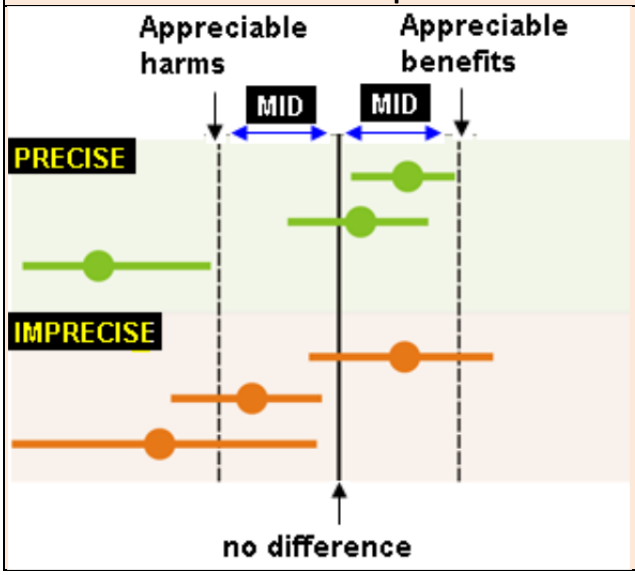
Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Imprecision

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered. The criteria applied for imprecision are based on the confidence intervals for pooled outcomes as illustrated in Figure 2.1 and outlined in Table 2.

Figure 1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results. Figure adapted from GRADEPro software.

Table 2-1: Criteria applied to determine precision

Criteria for downgrading an outcome for imprecision
The GDG decided the difference that is likely to be considered clinically important within epilepsy is 5%. The GDG discussed the issue of imprecision and the minimal important difference at length after it was raised by the stakeholder consultation. As stated in the ILAE guidelines "*For initial monotherapy trials, a 1998 guideline produced by the ILAE Commission on Antiepileptic Drugs estimated at 20% (not stated whether absolute or relative difference) the minimum outcome difference that should be regarded as clinically important.* *After extensive discussion, it was agreed that any relative difference >20% in primary outcome (effectiveness or efficacy) versus the comparator's arm (as defined in the study protocol) should be regarded as clinically significant*") . The GDG's view is that since seizures are a serious event, a 5% risk reduction or risk increase, whilst arbitrary, is a clinically significant difference in terms of the ability of the studies to detect a difference in outcome in epilepsy.

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

Quality element	Description
Limitations	This criterion relates to the methodological quality of cost, cost-effectiveness or net benefit estimates.
Applicability	This criterion relates to the relevance of the study to the specific guideline question and NICE Reference Case.

Table 2-3: Levels for limitations for economic evidence in NICE economic profile

Level	Description
Minor limitations	The study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.
Serious limitations	The study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness

Very serious limitations	The study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.

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

Level	Description
Directly applicable	The applicability criteria are met, or one or more criteria are not met but this is not likely to change the cost-effectiveness conclusions.
Partially applicable	One or more of the applicability criteria are not met, and this might possibly change the cost-effectiveness conclusions.
Not applicable	One or more of the applicability criteria are not met, and this is likely to change the cost-effectiveness conclusions.

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

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

2.8.1 Health economics methods

2004

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraisal by the health economist using a standard validated checklist.[42]. 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.

2012

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

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

a) The intervention dominated other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies) , or

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

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

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

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

- INB= (QALYs gained compared with a baseline drug x £20,000) minus the incremental cost compared with a baseline drug.

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

2.8.2 Literature review for health economics

A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

Full economic evaluations (cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence. The same population and intervention criteria were applied as in the clinical review.

Studies that only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorial, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country). Studies that were review previously as part of TA76 or TA79 were also excluded from this review.

[§] http://www.nice.org.uk/aboutnice/howwework/socialvaluejudgements/socialvaluejudgements.jsp

Remaining studies were prioritised for inclusion based on their relative applicability to the current UK NHS situation and development of this guideline, and the study limitations. For example, if a high quality, directly applicable UK analysis is available other less relevant studies may not be included. Where exclusions occurred on this basis, this is noted in the relevant evidence section.

Included papers were critically appraised by a health economist using the quality and applicability checklist outlined in the NICE guidelines manual 2009 [36]. If a paper was included, costs, outcomes and a description of its quality and applicability were presented in the economic evidence table with a brief description. Economic evidence tables for included studies are presented in Appendix M.

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

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

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

2.8.2.1 Cost-effectiveness modelling

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

a) Monotherapy for adults with newly diagnosed focal epilepsy

b) Adjunctive therapy for adults with refractory focal epilepsy

c) Monotherapy for children with newly diagnosed focal epilepsy

d) Adjunctive therapy for children with refractory focal epilepsy

e) Adjunctive therapy for adults with refractory generalised tonic-clonic seizures

The following general principles were adhered to:

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

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

2.9 Developing recommendations

2004

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.

2012

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

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

- Evidence tables of the clinical and economic evidence reviewed. All evidence tables are in appendix L.
- Summary of clinical evidence and quality (as presented in evidence review section in appendix N.
- A description of the methods and results of the cost-effectiveness analysis (appendices P - S)

Recommendations were drafted on the basis of this evidence whenever it was available.When clinical and economic evidence was poor or absent, the GDG drafted recommendations based on their clinical expertise. The GDG added supporting recommendations whenever it was necessary in order to improve clinical practice. The supporting recommendations were not derived from clinical questions and were based on GDG expert opinion.The development of the recommendations required several steps:

- Whenever possible, a preliminary draft recommendation was presented by NCGC staff after each summary of evidence presentation during GDG meetings. This draft was discussed and modified by the group to form the first draft recommendation.
- Where necessary, NCGC staff suggested modifications to the draft recommendations as a result of the discussion and in the light of NICE guidance on writing recommendations.
- Towards the end of the guideline development process, a list of all the draft recommendations was sent to the GDG members. The GDG members independently completed a consensus exercise to feedback comments and level of agreement on each recommendation. This procedure allowed the NCGC to verify the level of agreement between the GDG members.

- All GDG feedback was collated and circulated again to the GDG. The recommendations which did not have unanimous agreement were discussed again during a GDG meeting before being finalised.
- During the writing up phase of the guideline, the GDG could further refine each recommendation working in subgroups on each chapter.
- NCGC staff verified the consistency of all recommendations across the guideline.

2.10 Research Recommendations

2.10.1 Newly diagnosed seizures (focal and generalised) – monotherapy

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

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

Why this is important

Levetiracetam and other AEDs licensed for the treatment of focal and generalised seizures since publication of the original guideline 'The epilepsies' (NICE clinical guideline 20) in 2004 have not been evaluated as first-line monotherapy.

The research should include:

- a prospective randomised controlled trial
- all age groups
- subgroup analyses on seizure types and syndromes
- primary outcome of seizure freedom
- secondary outcomes, including seizure reduction, quality of life and cognitive outcome
- an attempt to obtain data on pharmaco-resistance.

2.10.2 Epilepsy syndromes

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

Why this is important

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

The research should include:

- multicentre randomised controlled comparative trials with centralised national data collection
- the ketogenic diet as one of the randomised treatments
- primary outcome of seizure freedom

- secondary outcomes, including seizure reduction, quality of life and cognitive outcome
- an attempt to obtain data on pharmaco-resistance
- the possibility of including all children with specific epilepsy syndromes for consideration in the trial.

2.10.3 Infantile spasms

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

Why this is important

The UK Infantile Spasms Study (UKISS) demonstrated 14-day outcome efficacy of steroids over vigabatrin, although this excluded children with tuberous sclerosis. This study provided no specific subgroup analysis based on the cause of the spasms. There was also no analysis on the effect of treatment lag (delay) on the study findings. Further data are available on behavioural outcomes with different treatments at 14 months and 4 years but with no analysis based on cause or treatment lag. Further developmental and cognitive outcomes would be useful, including response by specific cause and by treatment lag.

The research should include:

- prospective randomised design, including subgroup analyses based on both cause and treatment lag; this would require large numbers of patients and would need to be multicentre, possibly involving Western Europe
- EEG outcomes
- developmental status at presentation, and at follow-up
- an attempt to obtain data on pharmaco-resistance.

2.10.4 Treatment of convulsive status epilepticus (i.e. not just refractory)

What is the most effective and safest AED to treat:

- established (usually lasting longer than 30 minutes) convulsive status epilepticus
- refractory convulsive status epilepticus?

Why this is important

Convulsive status epilepticus (CSE) should be treated as an emergency. The most important aspect of treatment is to try to stop the seizure. Prompt, successful treatment of CSE avoids the need for admission to an intensive care unit (ICU). The most commonly used medication is phenytoin. This should be used with care and close monitoring because of the risk of hypotension and cardiac arrhythmia. Sodium valproate and levetiracetam are potentially as effective and safer alternatives but there are very limited comparative data.

CSE that is refractory to first-line treatment (RCSE) is rare and often complicated by irreversible neurological and intellectual sequelae, including death. Reasons for these complications include the underlying cause of RCSE, its duration and management. The majority, if not all patients with RCSE are managed in an ICU. There are no agreed drugs or treatment protocols for treating RCSE. The three most commonly used anticonvulsants are thiopental sodium, midazolam and propofol (propofol is rarely used in children). Data on treatment in children, young people and adults are

limited and anecdotal. A recently completed 2-year audit of everyone younger than 16 years with RCSE treated in an ICU in England, Wales and Scotland will provide unique epidemiological data on paediatric RCSE, its causes and current management. These data could be used to design a randomised controlled trial (RCT) of specific drug treatments and protocols.

The research should include:

- a multicentre randomised comparative trial of intravenous levetiracetam, sodium valproate and phenytoin in initial treatment of status epilepticus
- a multicentre RCT of treatment of refractory status epilepticus in ICUs, including midazolam and thiopental sodium (and propofol in adults)
- primary outcome of cessation of CSE
- secondary outcomes including recurrence within a designated period (probably 12 hours), mortality and morbidity
- cost data including treatment costs and days in intensive care.

2.10.5 AEDs and pregnancy

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

Why this is important

Pregnancy registers are increasing the data that are available on established AEDs; however, these registers may give malformation rates but do not provide controlled long-term data on neurodevelopmental outcome.

The research should include:

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

2.10.6 Ketogenic diet in adults

What is the effectiveness and tolerability of the ketogenic diet in adults with epilepsy?

Why is this important?

There are no data on the use of the ketogenic diet in adults. This may reflect the fact that the diet has been shown to be ineffective and the results unpublished, or, as is more likely, that the diet has never been used in this age group. In view of the numerous anecdotal and randomised controlled data demonstrating its effectiveness and that the number of antiepileptic drugs prescribed may be reduced as a result of this dietary approach in the paediatric epilepsies, it is appropriate to undertake a randomised controlled trial of ketogenic diet in adult patients with drug-resistant epilepsy.

The research should include:

- an initial pilot study of the feasibility and acceptability of the ketogenic diet in adults who are independent in activities of daily living and who have no learning difficulties

- if the pilot study indicates that the ketogenic diet is feasible and acceptable, a multi-centre randomised controlled study should be designed; this could evaluate one or more variants of the diet versus a normal diet
- primary outcome would be reduction in seizure-frequency
- secondary outcomes would include quality of life and reduction of antiepileptic drug burden
- cost data should include the total cost of the diet (including dietetic support), reduced drug costs and reduced admissions

2.11 Prioritisation of recommendations for implementation

2012

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

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

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

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

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

2004

The guideline was developed in parallel with two technology appraisals whose remit was to establish the clinical and cost effectiveness of newer drugs for adults and children with epilepsy and to provide guidance to the NHS in England and Wales[43] (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.

2012

The 2012 guideline partially updated the 2004 guideline and the two technology appraisals listed above. This update has reviewed additional published evidence on the AEDS included in the 2004 guideline technology appraisals. Therefore, the 2012 recommendations supersede those contained in the appraisals published in 2003. Further newer AEDs were also included in the 2012 guideline.

2.13 The relationship between the guideline and National Service Frameworks

2004

This guideline was developed at the same time as two relevant National Service Frameworks (NSFs): those for long-term conditions (focusing on neurological conditions) and children. NSFs have a different remit than clinical guidelines. A clinical guideline aims to 'assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances',[44] 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.

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

2004

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.

2.15 External review

2004

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.

2012

The external review process for this guideline remains as per the 2004 guideline. The 2012 guideline development process has followed the guidance contained within the NICE Guidelines Manual (2009).

In addition, the final draft of the guideline was reviewed by expert peer reviewers and an independent Guideline Review Panel (GRP) established by the Institute. A further step was added following the GRP review: an external pre-publication consultation process was undertaken to allow for factual inaccuracies to be corrected prior to publication

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

2.16 Level of evidence table

2004

Table 2.5 Level of evidence table

Hierarchy of evidence
Ia Systematic review or meta-analysis of randomised controlled trials
Ib 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 guidelines or Health Technology Appraisal programme

3 Key priorities for implementation

Diagnosis

- All children, young people and adults with a recent onset suspected seizure should be seen urgently[**] by a specialist[††]. This is to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]

Management

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

- All children, young people and adults with epilepsy should have a comprehensive care plan that is agreed between the person, their family and/or carers as appropriate, and primary and secondary care providers. [2004]

- The AED (anti-epileptic drug) treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person, their family and/or carers as appropriate. [2004]

Prolonged or repeated seizures and convulsive status epilepticus

- Administer buccal midazolam as first-line treatment in children, young people and adults with prolonged or repeated seizures. Administer rectal diazepam[g] if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam. [new 2012]

- Only prescribe buccal midazolam or rectal diazepam[g] for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures. [new 2012]

Special considerations for women and girls of childbearing potential

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

Review and referral

- All children, young people and adults with epilepsy should have a regular structured review. In children and young people, this review should be carried out at least yearly (but may be between 3 and 12 months by arrangement) by a specialist. In adults, this review should be carried out at least yearly by either a generalist or specialist, depending on how well the epilepsy is controlled and/or the presence of specific lifestyle issues. [2004]

- At the review, children, young people and adults should have access to: written and visual information; counselling services; information about voluntary organisations; epilepsy specialist

[**] The Guideline Development Group considered that 'urgently' meant being seen within 2 weeks.
[††] For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy. For children and young people, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy

nurses; timely and appropriate investigations; referral to tertiary services, including surgery if appropriate. [2004]

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

[‡‡] The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

4 Guidance

Note: see appendix K for further details of pharmacological treatment.

The recommendations made for pharmacological treatment have been placed together here in this summary of recommendations. The recommendations for each seizure type and epilepsy syndrome differ and should be read in conjunction with the relevant section of the guideline for clarity

The GDG is aware of the contraindications to prescribing carbamazepine to some people of Han Chinese or Thai origin. Recommendations in this section offer alternatives, and so no specific recommendations are made for these groups.

The GDG is also aware of specific issues with prescribing sodium valproate to girls and women of childbearing age. Recommendations in this section offer alternative prescribing options for this group.Recommendations 65, 73, 83, 207 and 212 also provide additional specific information of relevance when considering prescribing AEDs to women of childbearing age.

NICE has also issued guidance on the use of retigabine as an option for the adjunctive treatment of partial (the term focal has been used in this guideline) onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy in 'Retigabine for the adjunctive treatment of partial onset seizures in epilepsy' (NICE technology appraisal guidance 232).

General recommendations

1. Healthcare professionals should adopt a consulting style that enables the child, young person or adult with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs. [2004]
2. The diagnosis of epilepsy in adults should be established by a specialist medical practitioner with training and expertise in epilepsy. [2004]
3. The diagnosis of epilepsy in children and young people should be established by a specialist paediatrician with training and expertise in epilepsy. [2004]
4. It is recommended that all adults having a first seizure should be seen as soon as possible[•] by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]
5. It is recommended that all children and young people who have had a first non-febrile seizure should be seen as soon as possible[•] by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. [2004]
6. A detailed history should be taken from the child, young person or adult and an eyewitness to the attack, where possible, to determine whether or not an epileptic seizure is likely to have occurred. [2004]
7. The clinical decision as to whether an epileptic seizure has occurred should then be based on the combination of the description of the attack and different symptoms. Diagnosis should not be based on the presence or absence of single features. [2004]
8. The information that should be obtained from the adult and/or family or carer after a suspected seizure is contained in Appendix A. [2004]

[•] The Guideline Development Group considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.

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

10. In a child, young person or adult presenting with an attack, a physical examination should be carried out. This should address their cardiac, neurological and mental status, and should include a developmental assessment where appropriate. [2004]

11. It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations (see section 8) and/or referral to a tertiary epilepsy specialist[♣] (see recommendation 170) should be considered. Follow-up should always be arranged. [2004]

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

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

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

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

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

17. The EEG should not be used to exclude a diagnosis of epilepsy in a child, young person or adult in whom the clinical presentation supports a diagnosis of a non-epileptic event. [2004]

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

19. Children, young people and adults requiring an EEG should have the test performed soon[•] after it has been requested. [2004]

20. An EEG may be used to help determine seizure type and epilepsy syndrome in children, young people and adults in whom epilepsy is suspected. This enables them to be given the correct prognosis. [2004]

21. For children, young people and adults in whom epilepsy is suspected, but who present diagnostic difficulties, specialist investigations should be available. [2004]

22. Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful. [2004]

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

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

25. In children and young people, a sleep EEG is best achieved through sleep deprivation or the use of melatonin[♦]. [2004, amended 2012]

[♣] In this recommendation, 'centre' has been replaced with 'specialist' for consistency across recommendations.
[•] The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

26. Long-term video or ambulatory EEG may be used in the assessment of children, young people and adults who present diagnostic difficulties after clinical assessment and standard EEG. [2004]

27. 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 people. [2004]

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

29. In children, young people and adults presenting with a first unprovoked seizure, unequivocal epileptiform activity shown on EEG can be used to assess the risk of seizure recurrence. [2004]

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

31. MRI should be the imaging investigation of choice in children, young people and adults with epilepsy. [2004]

32. MRI is particularly important in those:

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

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

34. CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children and young people in whom a general anaesthetic or sedation would be required for MRI but not CT. [2004]

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

36. Children, young people and adults requiring MRI should have the test performed soon•. [2004]

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

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

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

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

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

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

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

♦ The licence for use of melatonin in the UK has changed since the recommendation was published in 2004. The recommendation has been updated accordingly and the footnote that contained the old information has been deleted.

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

44. Neuropsychological assessment should be considered in children, young people and adults in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory. [2004]

45. Referral for a neuropsychological assessment is indicated:

- when a child, young person or adult with epilepsy is having educational or occupational difficulties
- when an MRI has identified abnormalities in cognitively important brain regions
- when a child, young person or adult complains of memory or other cognitive deficits and/or cognitive decline. [2004]

46. Epileptic seizures and epilepsy syndromes in children, young people and adults should be classified using a multi-axial diagnostic scheme. The axes that should be considered are: description of seizure (ictal phenomenology); seizure type; syndrome and aetiology. [2004]

47. The seizure type(s) and epilepsy syndrome, aetiology, and co-morbidity should be determined, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment and persistence of seizures. [2004]

48. Children, young people and adults with epilepsy should be given information about their seizure type(s) and epilepsy syndrome, and the likely prognosis. [2004]

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

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

51. It is recommended that children, young people and adults should be treated with a single AED (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period. [2004]

52. 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 child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. [2004]

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

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

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

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

57. AED therapy should be considered and discussed with children, young people and adults and their family and/or carers as appropriate after a first unprovoked seizure if:
    - the child, young person or adult has a neurological deficit
    - the EEG shows unequivocal epileptic activity
    - the child, young person or adult and/or their family and/or carers consider the risk of having a further seizure unacceptable
    - brain imaging shows a structural abnormality. [2004]

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

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

60. AED therapy in children and young people should be initiated by a specialist. [2004]

61. 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 child, young person or adult and their family and/or carers as appropriate. [2004]

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

63. If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. [2004]

64. The needs of the child, young person or adult and their family and/or carers as appropriate should be taken into account when healthcare professionals take on the responsibility of continuing prescribing. [2004]

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

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

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

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

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

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

[♣] Please note that 'valproate' has been changed to 'sodium valproate' to be consistent with the terminology used in this update.

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

72. Adherence to treatment can be optimised with the following:

- educating children, young people and adults and their families and/or carers in the understanding of their condition and the rationale of treatment
- reducing the stigma associated with the condition (see also section 18.5)
- using simple medication regimens
- positive relationships between healthcare professionals, the child, young person or adult with epilepsy, and their family and/or carers. [2004]

73. 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 children, young people and adults with epilepsy, including school staff, social care professionals and others. [2004]

74. The risks and benefits of continuing or withdrawing AED therapy should be discussed with children, young people and adults, and their families and/or carers as appropriate, who have been seizure free for at least 2 years (see Appendix H[♣]). [2004]

75. The decision to continue or withdraw medication should be taken by the child, young person or adult, 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 children, young people and adults, and their family and/or carers as appropriate, should understand their risk of seizure recurrence on and off treatment. This discussion should take into account details of the child, young person or adult's epilepsy syndrome, prognosis and lifestyle. [2004]

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

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

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

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

80. When possible, choose which AED to offer on the basis of the presenting epilepsy syndrome. If the epilepsy syndrome is not clear at presentation, base the decision on the presenting seizure type(s). [new 2012]

81. Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person or adult, considers that this is not a concern. In the case of a child or young person this discussion may involve the parent or carer as well. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and 'British national formulary' (BNF; available at http://bnf.org.uk) on the bioavailability and

[♣] Appendix H of the full guideline provides tables for the prognosis for remission of seizures in adults.

pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations[•§§]. [new 2012]

82. If using carbamazepine, offer controlled-release carbamazepine preparations. [new 2012]

83. When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. [new 2012]

84. Maintain a high level of vigilance for treatment-emergent adverse effects (for example, bone health issues and neuropsychiatric issues[♣]) [new 2012]

Pharmacological management of focal seizures

85. Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures. [new 2012]

86. Levetiracetam is not cost effective at June 2011 unit costs[•]. Offer levetiracetam, oxcarbazepine or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Be aware of the teratogenic risks of sodium valproate (see recommendation 83).[new 2012]

87. Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 85 and 86). [new 2012]

88. Offer carbamazepine, clobazam[♠], gabapentin[♠], lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments (see recommendations 85 and 86) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

89. If adjunctive treatment (see recommendation 88) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [new 2012]

Pharmacological management of newly diagnosed generalised tonic-clonic seizures

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[•] Recommendations 1, 182, 184, 191 and 283 describe the principles of decision making and best practice in relation to effective and appropriate consultation between healthcare professionals and children, young people and adults with epilepsy.

[§§] In November 2013, the MHRA issued new advice about oral anti-epileptic drugs (AEDs) and switching between different manufacturers' products of a particular drug. Following a review of the available evidence, the Commission on Human Medicines (CHM) has classified AEDs into 3 categories depending on the level of potential concerns related to switching between different manufacturers' products. Consult the MHRA advice for more information.

[♣] Treatment with AEDs is associated with a small risk of suicidal thoughts and behaviour; available data suggest that the increased risk applies to all AEDs and may be seen as early as 1 week after starting treatment. Available from: www.mhra.gov.uk/PrintPreview/DefaultSplashPP/CON019574?DynamicListQuery=&DynamicListSortBy=xCreationDate&DynamicListSortOrder=Desc&DynamicListTitle=&PageNumber=1&Title=Antiepileptics%20&ResultCount=10

[•] Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. Cost taken from the National Health Service Drug Tariff for England and Wales, available at www.ppa.org.uk/ppa/edt_intro.htm

[♠] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

90. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed GTC seizures. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

91. Offer lamotrigine if sodium valproate is unsuitable. If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures. [new 2012]

92. Consider carbamazepine and oxcarbazepine♠ but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]

93. Offer clobazam♠, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with GTC seizures if first-line treatments (see recommendations 90, 91 and 92) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

94. If there are absence or myoclonic seizures, or if JME is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of absence seizures

95. Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence seizures. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

96. Offer lamotrigine♠ if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. [new 2012]

97. If two first-line AEDs (see recommendations 95 and 96) are ineffective in children, young people and adults with absence seizures, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine♠ or sodium valproate. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

98. If adjunctive treatment (see recommendation 97) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam♠, clonazepam, levetiracetam♠, topiramate♠ or zonisamide♠. [new 2012]

99. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of myoclonic seizures

100. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed myoclonic seizures, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

♠ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

101. Consider levetiracetam[♠] or topiramate[♠] if sodium valproate is unsuitable or not tolerated. Be aware that topiramate has a less favourable side-effect profile than levetiracetam and sodium valproate. [new 2012]

102. Offer levetiracetam, sodium valproate or topiramate[♠] as adjunctive treatment to children, young people and adults with myoclonic seizures if first-line treatments (see recommendations 100 and 101) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

103. If adjunctive treatment (see recommendation 102) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam[♠], clonazepam, piracetam or zonisamide[♠]. [new 2012]

104. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of tonic-clonic seizures

105. Offer sodium valproate as first-line treatment to children, young people and adults with tonic or atonic seizures. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

106. Offer lamotrigine[♠] as adjunctive treatment to children, young people and adults with tonic or atonic seizures if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2012]

107. Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 106) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide[♠] and topiramate[♠]. [new 2012]

108. Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of infantile spasms

109. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when an infant presents with infantile spasms. [new 2012]

110. Offer a steroid (prednisolone or tetracosactide[♠]) or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]

111. Offer vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide[♠]). Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]

Pharmacological management of Dravet syndrome

[♠] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

112. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Dravet syndrome. [new 2012]

113. Consider sodium valproate or topiramate♠ as first-line treatment in children with Dravet syndrome. [new 2012]

114. Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 113) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam♠ or stiripentol as adjunctive treatment. [new 2012]

115. Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of Lennox-Gastaut syndrome

116. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Lennox–Gastaut syndrome. [new 2012]

117. Offer sodium valproate as first-line treatment to children with Lennox–Gastaut syndrome. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

118. Offer lamotrigine as adjunctive treatment to children, young people and adults with Lennox–Gastaut syndrome if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2012]

119. Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 118) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. [new 2012]

120. Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. [new 2012]

121. Only offer felbamate♠ in centres providing tertiary epilepsy specialist care and when treatment with all of the AEDs listed in recommendations 119 and 120 has proved ineffective or not tolerated. [new 2012]

Pharmacological management of benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type)

122. Discuss with the child or young person, and their family and/or carers, whether AED treatment for benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) is indicated. [new 2012]

123. Offer carbamazepine♠ or lamotrigine♠ as first-line treatment to children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type). [new 2012]

124. Levetiracetam is not cost effective at June 2011 unit costs♣. Offer levetiracetam♠, oxcarbazepine♠, or sodium valproate (provided the acquisition cost of levetiracetam falls to at

♠ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

♣ Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. Cost taken from the National Health Service Drug Tariff for England and Wales, available at www.ppa.org.uk/ppa/edt_intro.htm

least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Be aware that carbamazepine and oxcarbazepine may exacerbate or unmask continuous spike and wave during slow sleep, which may occur in some children with benign epilepsy with centrotemporal spikes. Be aware of teratogenic risks of sodium valproate (see recommendation 83).[new 2012]

125. Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 123 and 124). [new 2012]

126. Offer carbamazepine♠, clobazam♠, gabapentin♠, lamotrigine♠, levetiracetam♠, oxcarbazepine , sodium valproate or topiramate as adjunctive treatment to children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) if first-line treatments (see recommendations 123 and 124) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

127. If adjunctive treatment (see recommendation 126) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate♠, lacosamide♠ , phenobarbital, phenytoin, pregabalin♠, tiagabine♠, vigabatrin♠ and zonisamide♠. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [new 2012]

Pharmacological management of idiopathic generalised epilepsy

128. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed IGE, particularly if there is a photoparoxysmal response on EEG. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

129. Offer lamotrigine♠ if sodium valproate is unsuitable or not tolerated. Be aware that lamotrigine can exacerbate myoclonic seizures. If JME is suspected see recommendations 134 and 135.[new 2012]

130. Consider topiramate♠ but be aware that it has a less favourable side-effect profile than sodium valproate and lamotrigine♠. [new 2012]

131. Offer lamotrigine♠, levetiracetam♠, sodium valproate or topiramate♠ as adjunctive treatment to children, young people and adults with IGE if first-line treatments (see

♠ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

recommendations 128, 129 and 130) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

132. If adjunctive treatment (see recommendation 131) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam[♠], clonazepam or zonisamide[♠]. [new 2012]

133. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of juvenile myoclonic epilepsy

134. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed JME, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

135. Consider lamotrigine[♠], levetiracetam[♠], or topiramate[♠] if sodium valproate is unsuitable or not tolerated. Be aware that topiramate has a less favourable side-effect profile than lamotrigine, levetiracetam and sodium valproate, and that lamotrigine may exacerbate myoclonic seizures. [new 2012]

136. Offer lamotrigine[♠], levetiracetam, sodium valproate or topiramate[♠] as adjunctive treatment to children, young people and adults with JME if first-line treatments (see recommendations 134 and 135) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

137. If adjunctive treatment (see recommendation 136) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam[♠], clonazepam or zonisamide[♠]. [new 2012]

138. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of generalised tonic-clonic seizures only

139. Offer lamotrigine or sodium valproate as first-line treatment to children, young people and adults with epilepsy with GTC seizures only. If they have suspected myoclonic seizures, or are suspected of having JME, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

140. Consider carbamazepine and oxcarbazepine[♠] but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]

141. Offer clobazam[♠], lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with epilepsy with GTC seizures only, if

[♠] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

first-line treatments (see recommendation 139 and 140) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

Pharmacological management of childhood absence epilepsy, juvenile absence epilepsy and other absence syndromes

142. Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence syndromes. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

143. Offer lamotrigine♠ if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. [new 2012]

144. If two first-line AEDs (see recommendations 142 and 143) are ineffective in children, young people and adults with absence epilepsy syndromes, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine♠ or sodium valproate. Be aware of the teratogenic risks of sodium valproate (see recommendation 83). [new 2012]

145. If adjunctive treatment (see recommendation 144) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam♠, clonazepam, levetiracetam♠, topiramate♠ or zonisamide♠. [new 2012]

146. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]

Pharmacological management of other epilepsy sydromes

147. Refer to a tertiary paediatric epilepsy specialist all children and young people with continuous spike and wave during slow sleep, Landau–Kleffner syndrome or myoclonic-astatic epilepsy. [new 2012]

General recommendations continued

148. Care must be taken to secure the child, young person or adult's airway and assess his or her respiratory and cardiac function. [2004]

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

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

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

152. If either the whole protocol or intensive care is required the tertiary service should be consulted. [2004]

153. An individual treatment pathway should be formulated for children, young people and adults who have recurrent convulsive status epilepticus. [2004]

154. Give immediate emergency care and treatment to children, young people and adults who have prolonged (lasting 5 minutes or more) or repeated (three or more in an hour) convulsive seizures in the community. [2012]

155. Only prescribe buccal midazolam or rectal diazepam[♠] for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures. [new 2012]

156. Administer buccal midazolam as first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Administer rectal diazepam[♠] if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam. [new 2012]

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

- the seizure is continuing 5 minutes after the emergency medication has been administered
- the person has a history of frequent episodes of serial seizures or has convulsive status epilepticus, or this is the first episode requiring emergency treatment **or**
- there are concerns or difficulties monitoring the person's airway, breathing, circulation or other vital signs. [new 2012]

158. For children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus) who are in hospital, immediately:

- secure airway
- give high-concentration oxygen
- assess cardiac and respiratory function
- check blood glucose levels **and**
- secure intravenous access in a large vein.

See also the suggested protocols in appendix K. [new 2012]

159. Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). Administer intravenous diazepam if intravenous lorazepam is unavailable, or use buccal midazolam if unable to secure immediate intravenous access. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment). See also the suggested protocols in appendix K. [new 2012]

160. If seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). See also the suggested protocols in appendix K. [new 2012]

161. Follow the suggested protocols in appendix K for treating refractory convulsive status epilepticus in secondary care. [2012]

162. Administer intravenous midazolam[♠], propofol[♠] or thiopental sodium[♠] to treat adults with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and

[♠] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

critical life systems support are required. See also the suggested protocols in appendix K. [new 2012]

163. Administer intravenous midazolam♠ or thiopental sodium♠ to treat children and young people with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and critical life systems support are required. See also the suggested protocols in appendix K. [2012]

164. Non-convulsive status epilepticus is uncommon and management is less urgent. A suggested guideline can be found in appendix K. [2004]

165. All children, young people and adults with epilepsy should have access via their specialist to a tertiary service when circumstances require. [2004]

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

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

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

169. If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, children, young people and adults should be referred to tertiary services soon• for further assessment. Referral should be considered when one or more of the following criteria are present:

- the epilepsy is not controlled with medication within 2 years
- management is unsuccessful after two drugs
- the child is aged under 2 years
- a child, young person or adult experiences, or is at risk of, unacceptable side effects from medication
- there is a unilateral structural lesion
- there is psychological and/or psychiatric co-morbidity
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. [2004]

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

171. Behavioural or developmental regression or inability to identify the epilepsy syndrome in a child, young person or adult should result in immediate referral to tertiary services. [2004]

172. Children, young people and adults with specific syndromes such as Sturge–Weber syndrome, the hemispheric syndromes, Rasmussen's encephalitis and hypothalamic hamartoma should be referred to a tertiary epilepsy service. [2004]

♠ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

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

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

174. Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]

175. Psychological interventions (relaxation, cognitive behaviour therapy, biofeedback) may be used in conjunction with AED therapy in adults where either the person 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 people. [2004]

176. Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children and young people with drug-resistant focal epilepsy. [2004]

177. Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet. [new 2012]

178. 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 focal seizures[♦] (with or without secondary generalisation) or generalised seizures. [2004, amended 2012]

179. Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures[♦] (with or without secondary generalisation) or generalised seizures[♥]. [2004, amended 2012]

180. Children, young people and adults 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

[♣] In this recommendation, 'centre' has been replaced with 'service' for consistency across recommendations.

[♦] In this recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.

[♥] Evidence from 'Vagus nerve stimulation for refractory epilepsy in children', NICE interventional procedure guidance 50 (2004).

- importance of disclosing epilepsy at work, if relevant (if further information or clarification is needed, voluntary organisations should be contacted).
- road safety and driving
- prognosis
- sudden death in epilepsy (SUDEP)
- status epilepticus
- lifestyle, leisure and social issues (including recreational drugs, alcohol, sexual activity and sleep deprivation)
- family planning and pregnancy
- voluntary organisations, such as support groups and charitable organisations, and how to contact them. [2004]

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

182. Information should be provided in formats, languages and ways that are suited to the child, young person or adult's requirements. Consideration should be given to developmental age, gender, culture and stage of life of the person. [2004]

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

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

185. Checklists should be used to remind children, young people and adults, and healthcare professionals, about information that should be discussed during consultations. [2004]

186. Everyone providing care or treatment for children, young people and adults with epilepsy should be able to provide essential information. [2004]

187. The child, young person or adult 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 child, young person or adult and/or their family and/or carers are met. [2004]

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

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

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

191. Children, young people and adults with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). [2004]

192. Children, young people and adults and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. [2004]

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

194. The risk of SUDEP can be minimised by:

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

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

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

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

198. Information should be provided to children, young people and adults 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 informed consent is obtained. [2004]

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

200. Information about contraception, conception, pregnancy, or menopause should be given to women and girls in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with women and girls with epilepsy. These may include her family and/or carers. [2004]

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

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

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

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

205. All women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women and girls taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. [2004]

206. Prescribers should consult individual drug advice in the SPC and the BNF (available at http://bnf.org)* when prescribing AEDs for women and girls who are breastfeeding. The decision regarding AED therapy and breastfeeding should be made between the woman or girl and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. [2004, amended 2012]

207. Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. [new 2012]

208. Be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of present and future childbearing potential. [2012]

209. Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalised tonic–clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of each AED, avoiding polytherapy if possible. [new 2012]

210. Discuss with women and girls who are taking lamotrigine that the simultaneous use of any oestrogen-based contraceptive can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When a woman or girl starts or stops taking these contraceptives, the dose of lamotrigine may need to be adjusted. [new 2012]

211. Do not routinely monitor AED levels during pregnancy. If seizures increase or are likely to increase, monitoring AED levels (particularly levels of lamotrigine and phenytoin, which may be particularly affected in pregnancy) may be useful when making dose adjustments. [new 2012]

212. 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 (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)
- specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy (see recommendation 211) [2012]

213. Refer to the SPC and BNF (available at http://www.bnf.org) for individual drug advice on the interactions between AEDs and hormonal replacement and contraception. [new 2012]

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

* In this recommendation, the original referral to appendix 5 of the BNF has been removed and replaced with more up-to-date source reference material because this appendix no longer exists and has therefore become obsolete since the original guideline was published in 2004.

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

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

217. If a woman or girl taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, guidance about dosage should be sought from the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012]

218. The progestogen[•]-only pill is not recommended as reliable contraception in women and girls taking enzyme-inducing AEDs. [2004, amended 2012]

219. The progestogen[•] implant is not recommended in women and girls taking enzyme-inducing AEDs. [2004, amended 2012]

220. The use of additional barrier methods should be discussed with women and girls taking enzyme-inducing AEDs and oral contraception or having depot injections of progestogen. [2004, amended 2012]

221. If emergency contraception is required for women and girls taking enzyme-inducing AEDs, the type and dose of emergency contraception should be in line with the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012]

222. Women and girls 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 and girls without epilepsy. [2004]

223. Care of pregnant women and girls should be shared between the obstetrician and the specialist. [2004]

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

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

226. All women and girls on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. [2004]

227. Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women and girls who plan to stop AED therapy (see section 10.2.6). [2004]

228. Women and girls 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. [2004]

[•] In this recommendation, 'progesterone' has been replaced with 'progestogen' to reflect a change in terminology since the original guideline was published in 2004.

229. Women and girls should be reassured that there is no evidence that focal[♦], absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury. [2004, amended 2012]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

♦ In this recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.

245. In the child or young person presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. [2004]

246. In making a care plan for a child, young person or adult with learning disabilities and epilepsy, particular attention should be paid to the possibility of adverse cognitive and behavioural effects of AED therapy. [2004]

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

248. Enable children, young people and adults who have learning disabilities, and their family and/or carers where appropriate, to take an active part in developing a personalised care plan for treating their epilepsy while taking into account any comorbidities. [new 2012]

249. Ensure adequate time for consultation to achieve effective management of epilepsy in children, young people and adults with learning disabilities. [new 2012]

250. Do not discriminate against children, young people and adults with learning disabilities, and offer the same services, investigations and therapies as for the general population. [new 2012]

251. Every therapeutic option should be explored in children, young people and adults with epilepsy in the presence or absence of learning disabilities. [2004]

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

253. All children, young people and adults 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 child, young person or adult are balanced with the role of the carer. [2004]

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

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

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

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

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

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

260. 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 chapter 12). [2004]

261. The diagnosis and management of epilepsy should be reviewed during adolescence. [2004]

262. Do not discriminate against older people, and offer the same services, investigations and therapies as for the general population. [new 2012]

263. Pay particular attention to pharmacokinetic and pharmacodynamic issues with polypharmacy and comorbidity in older people with epilepsy. Consider using lower doses of AEDs and, if using carbamazepine, offer controlled-release carbamazepine preparations. [new 2012]

264. Children, young people and adults 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 a person's needs are appropriately met. [2004]

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

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

267. Children, young people and adults with epilepsy should have a regular structured review and be registered with a general medical practice. [2004]

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

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

270. Epilepsy specialist nurses (ESNs) should be an integral part of the network of care of children, young people and adults 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 child, young person or adult, families, carers and, in the case of children, others involved in the child's education, welfare and well-being. [2004]

271. Children, young people and adults with epilepsy should have an accessible point of contact with specialist services. [2004]

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

273. 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 person or clinician view the epilepsy as inadequately controlled. [2004]

274. Adults with well-controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist. [2004]

275. Children and young people should have a regular structured review with a specialist. [2004]

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

277. At the review, children, young people and adults should have access to: written and visual information; counselling services; information about voluntary organisations; epilepsy specialist nurses; timely and appropriate investigations; referral to tertiary services including surgery, where appropriate. [2004]

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

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

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

281. Protocols should be in place that ensure proper assessment in the emergency setting for children, young people and adults presenting with an epileptic seizure (suspected or confirmed). [2004]

282. Children, young people and adults with epilepsy and their families and/or carers should be empowered to manage their condition as well as possible. [2004]

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

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

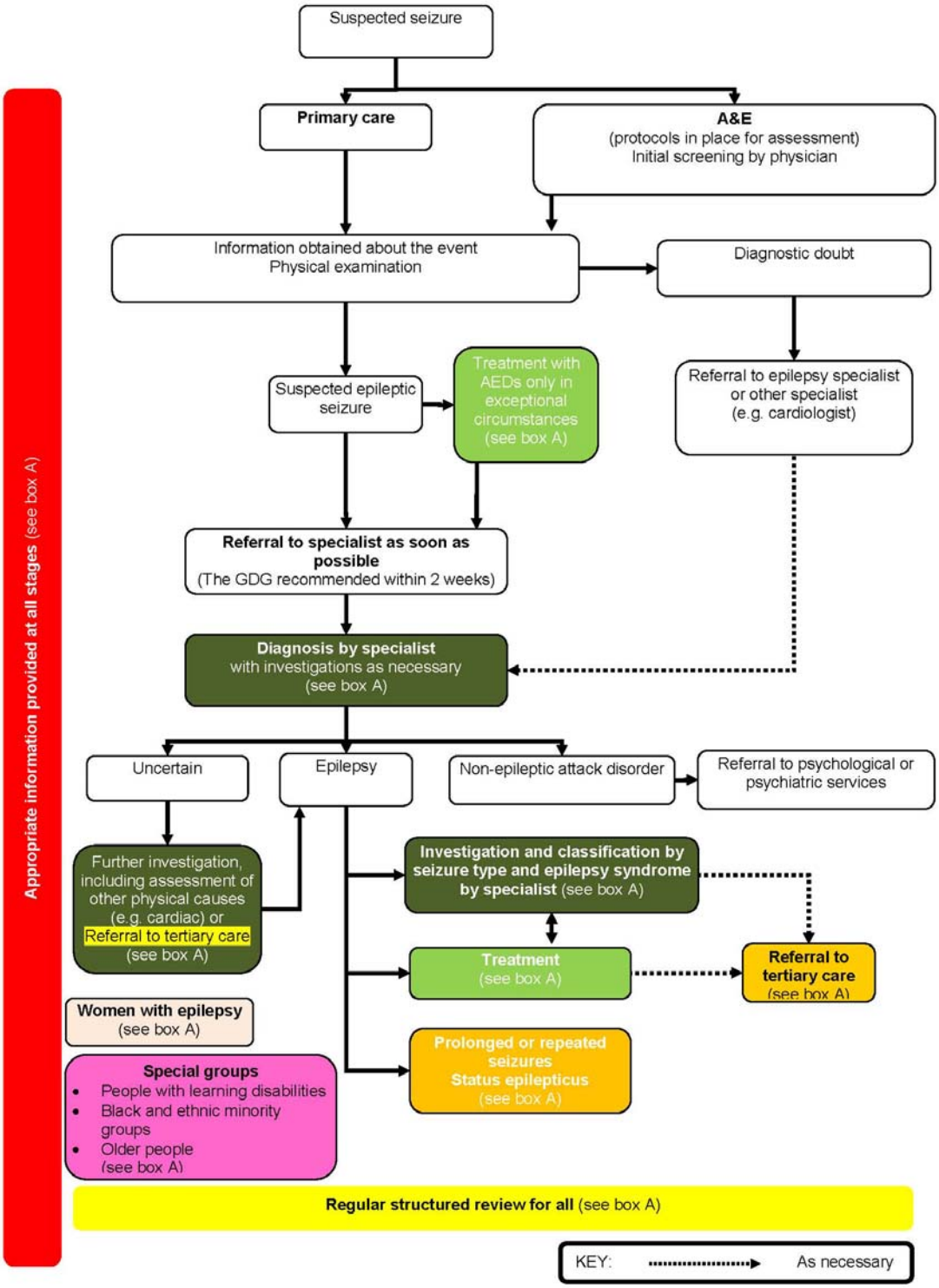
[♣] For adults, a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy. For children and young people, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.

285. Healthcare professionals should highlight the Expert Patients Programme (www.expertpatients.co.uk•) to children, young people and adults with epilepsy who wish to manage their condition more effectively. [2004, amended 2012]

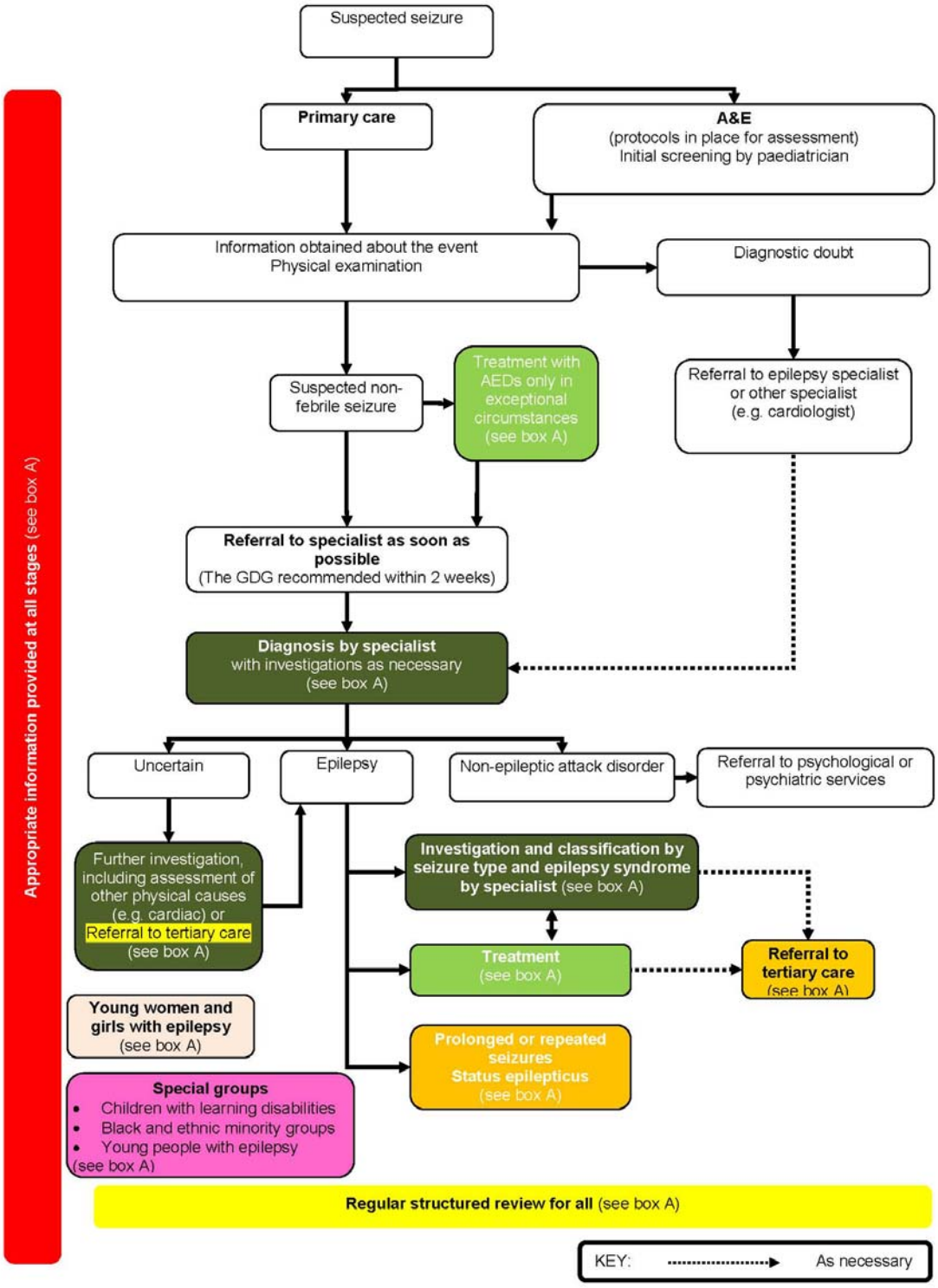
• This web address has changed since the recommendation was published in 2004 and has been updated.

4.1.1 Outline epilepsy care algorithms

Outline care algorithm for adults



Outline care algorithm for children


Suspected seizure
Primary care
A&E
(protocols in place for assessment)
Initial screening by paediatrician
Information obtained about the event
Physical examination
Diagnostic doubt
Suspected non-febrile seizure
Treatment with AEDs only in exceptional circumstances (see box A)
Referral to epilepsy specialist or other specialist (e.g. cardiologist)
Referral to specialist as soon as possible
(The GDG recommended within 2 weeks)
Diagnosis by specialist
with investigations as necessary
(see box A)
Uncertain
Epilepsy
Non-epileptic attack disorder
Referral to psychological or psychiatric services
Further investigation, including assessment of other physical causes (e.g. cardiac) or Referral to tertiary care (see box A)
Investigation and classification by seizure type and epilepsy syndrome by specialist (see box A)
Treatment
(see box A)
Referral to tertiary care
(see box A)
Young women and girls with epilepsy
(see box A)
Prolonged or repeated seizures
Status epilepticus
(see box A)
Special groups
Children with learning disabilities
Black and ethnic minority groups
Young people with epilepsy
(see box A)
Regular structured review for all (see box A)
Appropriate information provided at all stages (see box A)
KEY:
As necessary

Box A Cross Reference for algorithms	**Page Number**
Treatment with AEDs only in exceptional circumstances	136
Diagnosis and investigations	87 and 93
Further investigations	98, 102, 103, 104, 105, 114, 116
Investigations and classification by seizure type and epilepsy	119
Referral to tertiary care	477
Treatment	130
Prolonged or repeated seizures; status epilepticus	443
Women and girls with epilepsy	504
Special groups	544, 558, 563, 572
Regular structured review	574, 577
Appropriate information	493

5 Audit Criteria

2004

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.

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

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

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.

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.

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

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

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

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

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

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

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

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

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

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

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

The records show that if individuals were referred to tertiary services, referral was appropriate.

The records show that all individuals who have indications for referral to tertiary services were referred.

6 Principle of decision making

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

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

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

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

British Epilepsy Association 2000[45]

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.[45]

7 Diagnosis

7.1 Introduction

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

7.2 Establishing the diagnosis of epilepsy

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

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

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

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

Evidence statement

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

Details

An adequate diagnosis of epilepsy requires differentiation between seizures and other causes of transient neurological disturbance and collapse; differentiation between acute symptomatic and unprovoked epileptic seizures; and, in people with epilepsy, classification of the disorder and identification of the cause so as to optimise treatment.[46]

Secondary evidence

[***] The Guideline Development Group considered that with a recent onset suspected seizure, referrals should be urgent, meaning that patients should be seen within 2 weeks.

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

Primary evidence

Smith 1999[5]

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

Scheepers 1998[47]

In another population study, 49 of 214 individuals with a primary diagnosis of epilepsy were subsequently found to be misdiagnosed. Of these, 20 were found to have had cardiovascular or cerebrovascular pathology. Seven had only ever experienced one seizure and a further 10 were found to have underlying psychopathology.

7.3 Key features of the history and examination that allow epilepsy to be differentiated from other diagnoses in adults and children

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

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

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

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

10. **In a child, young person or adult presenting with an attack, a physical examination should be carried out. This should address their cardiac, neurological and mental status, and should include a developmental assessment where appropriate. [2004]**

11. **It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations (see section 8) and/or referral to a tertiary epilepsy specialist[†††] (see recommendation 170) should be considered. Follow-up should always be arranged. [2004]**

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

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)

[†††] In this recommendation 'centre' has been replaced with 'specialist' for consistency across the recommendations.

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.[48,49] Unfortunately it is difficult to prepare an evidence-based review on the clinical diagnosis of epilepsy for reasons discussed below.

Secondary evidence

AHRQ 2001[50]

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:

- '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 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.'[50]

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. [51,52]

- Berg and colleagues[53,54] reported that 609 of 613 children were assigned a syndromic diagnosis on the basis of clinical features.

- Arts, Geerts, Brouwer, and colleagues[55] reporting on 466 children suggested the history alone yielded a 29 percent sensitivity and 89 percent specificity.
- Hoefnagels, Padblerg, Overweg, and colleagues[52] noted that it was impossible to find a gold standard for the diagnosis of epilepsy and therefore developed their own to distinguish epilepsy from syncope. Sensitivity and specificity of several components of a history were computed, e.g., particular symptoms before, during, and after the paroxysmal event. Those before the event had the highest sensitivity (88% to 98%), and those during the event, the highest specificity (64% to 94%).
- Camfield, Camfield, Dooley and colleagues[51] 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 (focal seizure associated with increased risk). Neither the sleep-wake status at the first seizure nor a history of febrile seizures predicted recurrence. In three additional retrospective studies, the utility of various interventions in diagnosis and/or prediction of recurrence was reported.
- Ambrosetto, Giovanardi, and Tassinari[56] reported on history (and EEG findings) in 72 individuals and concluded that only generalized seizures as the sole ictal phenomenon, and a long interval between the first and second seizures, were predictive of seizure frequency subsequently.

Other primary papers

Sheldon 2002[57]

Since the AHRQ review[50], 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.[57]

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.[44]

They propose the use of the following questions:

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

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

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

- Have you ever had light-headed spells?
- At times do you sweat before your spells?

- Is prolonged sitting or standing associated with your spells?

7.4 What are the key features of the history and examination that allow an epileptic seizure to be differentiated from other causes of attack disorder in adults?

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

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

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

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

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

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

Evidence statements

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

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

Details

Methodological issues

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

A review of the evidence, however, identified papers of limited validity (case series) and questionable generalisability. Three papers were identified that looked at the use of home video recordings as an aid to the diagnosis of epilepsy in adults [58] and children.[59,60] 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.[61]

Primary evidence

Newmark 1981[58]

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 'secondarily generalised tonic-clonic seizures' was made by analysis of the home video-tape.

Sheth 1994[59]

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 phenobarbital was prescribed. The seizures continued and a repeat video 6 weeks later revealed the diagnosis to be 'infantile masturbation' and therapy was discontinued.

Woody 1985[60]

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 focal seizure' and 'reflex micturition epilepsy').

Health economics

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

8 Investigations

8.1 Introduction

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

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

8.2 The role of EEG in making a diagnosis of epilepsy

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

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

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

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

17. The EEG should not be used to exclude a diagnosis of epilepsy in a child, young person or adult in whom the clinical presentation supports a diagnosis of a non-epileptic event. [2004]

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

19. Children, young people and adults requiring an EEG should have the test performed soon[‡‡‡] after it has been requested. [2004]

Evidence statements

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

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

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

[‡‡‡] The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

Details

A recent definition of what constitutes a standard/'routine' interictal EEG has been provided in guidelines produced by the International League Against Epilepsy.[62] 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.[62]

Secondary evidence

Linzer 1997[63]

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

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

Fowle 2000[64]

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.[64] Thus, the EEG may be abnormal in normal people (in one study of male RAF personnel who are all 'screened' using EEG, 0.5% (69/13658), of the sample had 'epileptiform' discharges[65]). It may also be normal in people with epilepsy.

Gilbert 2000[66]

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 2001[50]

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. [50]

Primary evidence

The primary papers reviewed here had methodological deficiencies according to criteria for diagnostic tests proposed by the Evidence Based Medicine Working Group. [49,67]

Goodin 1984[68]

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

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

Table 8.1 Results from a review of 948 individuals with various non-epileptic neurological and psychiatric disorders referred for EEG and 764 individuals with epilepsy

A) Results of interictal EEG		
	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[§§§]	
Likelihood ratio for negative test	0.5[****]	

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

The results can be interpreted as follows. Epileptiform activity in the EEG is specific, but not sensitive, for the diagnosis of epilepsy. A positive interictal EEG can be used to help confirm the diagnosis of epilepsy but a negative result cannot be used to rule out the diagnosis of epilepsy.

Hoefnagels 1991[52]

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%)

[§§§] Result defined as a large increase in pre-test to post-test probability
[****] Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)

or syncope (62%). Their findings for the test characteristics of interictal EEG are presented below (presented in this form in the paper).

Table 8-2: Results of EEG in 118 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)[§§§§]	7.3[††††] (2.6 – 20.3)	
Likelihood ratio for negative test (CI)	0.6[‡‡‡‡] (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 2000[69]

A Canadian study explored the question as to how often routine EEG results can be correctly predicted from the EEG requisition form in children.

Five hundred consecutive initial EEG requests were examined (child mean age 5 years 11 months). Based only on the requisition (demographics, referring physician, and reason for EEG), the authors coded their prediction of the result and then the actual result. When results were discordant from prediction, a judgment was made about the potential importance of the result.

Overall, EEG results were correctly predicted in 81%. Prediction for all non-epilepsy reasons was accurate in 91% (n=320). The highest rate of correct prediction was in the group with non-epileptic paroxysmal disorders. Children in this category were almost always (99%, 157/158) predicted to have a normal EEG. In contrast, for children clinically suspected as having epilepsy the correct EEG findings were correctly predicted in 59% of cases (n=141) (comparison of prediction for paroxysmal vs epileptic disorders, p<0 0001 chi squared).

Jan 2002[70]

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

[††††] Result defined as a moderate increase in pre-test to post-test probability
[‡‡‡‡] Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)
[§§§§] CI- confidence interval

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) 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.[70]

The results have been extracted from the paper and tabulated below (only subgroups of seizure versus non-epileptic paroxysmal event included: 44%, 194/438 of all EEG requests).

Table 8-3: Results of EEG for seizures vs non-epileptic paroxysmal events

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[*****] 0.76[†††††]	
Likelihood ratio for negative test		

Stroink 2003[71]

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.

[*****] Result defined as a large increase in pre-test to post-test probability
[†††††] Result defined as a small decrease in pre-test to post-test probability (of uncertain clinical importance)

8.2.2 How good is the EEG at differentiating between individuals who have different epilepsy seizure types and epilepsy syndromes?

20. An EEG may be used to help determine seizure type and epilepsy syndrome in children, young people and adults in whom epilepsy is suspected. This enables them to be given the correct prognosis. [2004]

The standard EEG can help classify individuals with a clinical diagnosis of an epileptic seizure into different epilepsy seizure types and epilepsy syndromes. (III)

Details

Secondary evidence

Hirtz 2000[72]

An evidence-based review of approaches for evaluating a first non-febrile seizure in children was identified. This stated that the majority of studies confirmed that an EEG helps in determination of seizure type and epilepsy syndrome in children.

Primary evidence

King 1998[73]

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; 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 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%); focal epilepsy (58%); and unclassified (19%).

8.2.3 How can the diagnostic yield of the standard interictal EEG be improved?

21. For children, young people and adults in whom epilepsy is suspected, but who present diagnostic difficulties, specialist investigations should be available. [2004]

22. Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful. [2004]

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

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

25. In children and young people, a sleep EEG is best achieved through sleep deprivation or the use of melatonin[‡‡‡‡‡]. [2004, amended 2012]

Evidence

There is insufficient high quality evidence to determine whether performing an EEG within the first 24 hours after a seizure increases the likelihood of obtaining epileptiform activity. (III)

Repeating a standard EEG in a selected adult population has been shown to increase the likelihood of obtaining epileptiform activity. (III)

Recording of the EEG whilst asleep or after sleep deprivation increases the likelihood of obtaining epileptiform activity. (III)

The use of melatonin may be used to induce sleep in children who are to undergo a sleep EEG. (III)

Details

As reviewed in the preceding section, the sensitivity of standard interictal EEG is low. This section reviews the evidence for increasing the diagnostic yield of EEG by the following additional techniques:

- early recording of EEG after seizure;
- repeatedly performing EEGs
- sleep: sleep EEGs and sleep deprivation EEGs.

The following general reviews were consulted.[50,64,74] Specific review articles are discussed below.

8.2.3.1 Early recording of EEG after seizure

Secondary evidence

No systematic reviews were identified.

Primary evidence

King 1998[73]

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; 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 licence for use of melatonin in the UK has changed since the recommendation was published in 2004. The recommendation has been updated accordingly and the footnote that contained the old information has been deleted.

The first EEG was performed within 12 hours of the seizure in 89 (30%) individuals, between 12–24 hours in 67 (22%) individuals, and after more than 24 hours in 144 (48%) individuals. Epileptiform abnormalities were observed in 80 (51%) of the 156 who had an EEG within the first 24 hours, compared with 49 (34%) of the 144 who had a later EEG (95% CI for difference in proportions 6%–28%).

Sundaram 1990[75]

Sundaram and colleagues investigated various factors affecting interictal spike discharges in the EEGs of 203 consecutive cases with seizures.

Participants were all adults (aged 16 years and over) with definite or suspected seizures who were referred for an EEG. Adults with a history suggesting non-specific blackouts, syncope, pseudoseizures or alcohol withdrawal seizures, undergoing assessment for surgery or those who had any surgery for epilepsy were excluded.

Interictal spike discharges were correlated with age, number of seizures in the previous 12 months, timing of the EEG with relation to the last seizure, AED treatment, aetiology, and neurological status. Blinding was not documented.

77% (n=27/35) of those EEGs performed within 2 days of the last seizure showed ISDs compared with 33% (n=5/15) for EEGs within 2 to 7 days, and 41% (n=62/153) for EEGs more than 7 days after the last seizure.

8.2.3.2 Repeatedly performing EEGs

Secondary evidence

No systematic reviews were identified.

Primary evidence

Salinsky 1987[76]

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 focal seizures).

In 50% of adults with IEA, the abnormality was present on the first EEG, in 84% by the third EEG and in 92% by the fourth EEG.

8.2.3.3 Sleep and sleep deprivation EEGs

A narrative review which considered the earlier literature[77] and a recent critical review of the literature[78] 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.[64]

Two prospective studies of the role of sleep and sleep deprivation were identified, both included in the Agency for Healthcare Research & Quality systematic review. [50]

Secondary evidence

No systematic reviews were identified.

Primary evidence

Carpay 1997[79]

A prospective Dutch study aimed to assess the diagnostic yield of a repeated EEG after partial sleep deprivation in children and adolescents with one or more seizures who had previously had a standard EEG.

The study population was 552 children (age: range 1 month – 16 years; mean 6 years) with one or more newly diagnosed seizures. Intermittent photic stimulation was performed on all EEGs, and hyperventilation was induced when the child was co-operative. A routine interictal EEG was recorded. When the standard-EEG was classified to be without epileptiform activity, a sleep deprived-EEG was recorded by using an age-dependent protocol for sleep deprivation. The assessor of the EEGs was blinded to the clinical assessment.

Fifty six percent (309/552) of the sample had a positive standard-EEG and 44% (243/552) had an EEG without epileptiform activity. In 177 (73% of all eligible children) of these negative cases, sleep deprived-EEGs were recorded. Sleep deprived-EEGs added 11% (61/552) more diagnoses to the 56% of children with epileptiform activity on the standard-EEG (67% in total).

King 1998[73]

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; focal epilepsy or seizure unclassified. The authors attempted to obtain an EEG within 24 hours of the seizure. Where the EEG was negative, a sleep-deprived EEG was done. MRI was done electively. It is not clear if the EEG assessor was blinded to the clinical assessment.

Epileptiform abnormalities were shown in 43% (129/300) of the first EEG records. A majority of those with a negative first EEG (92%, 158/171) underwent a sleep-deprived EEG. A sleep-deprived EEG added 18% (55/300) more diagnoses to the 43% of those with epileptiform activity on the first EEG (61% in total).

Schreiner 2003[80]

Schreiner and Pohlmann-Eden aimed to evaluate the predictive value of standard EEG and EEG with sleep deprivation for seizure recurrence in adults after a first unprovoked seizure. 157 adults were included and were aged between 17 and 84 years. 61.8% were male. A standard EEG was performed within 48 hours of the first seizure. A sleep deprived EEG was performed 3 to 7 days after the first seizure for those in whom the standard EEG was normal or was inconclusive.

46 adults (29.3%) had a normal EEG. Of the 60 whose initial EEG was normal or was inconclusive, the sleep deprived EEG showed abnormalities in 9 adults. Conversely, in 10 adults, sleep deprived EEG did not detect abnormalities already identified by the standard EEG.

8.2.3.4 What is the role of melatonin for children undergoing a sleep EEG?

In children, sleep EEGs have traditionally been undertaken by depriving children of sleep the night before the EEG study. This procedure, however, has been shown to be of limited acceptability to parents of children with epilepsy.[81] As an alternative, children can be given oral melatonin to induce sleep.[82]

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

8.2.4 What are the roles of long-term video-EEG and ambulatory EEG?

26. Long-term video or ambulatory EEG may be used in the assessment of children, young people and adults who present diagnostic difficulties after clinical assessment and standard EEG. [2004]

Evidence statements

Long-term video-EEG and ambulatory EEG can help differentiate between epileptic and non-epileptic seizures in individuals who present diagnostic difficulties following clinical assessment and standard EEG. (III)

Long-term video-EEG and ambulatory EEG can help classify seizure type and seizure syndrome in individuals who present diagnostic difficulties following clinical assessment and standard EEG. (III)

Details

Inpatient video-EEG has an important role in the diagnosis of epilepsy when the clinical history and standard EEG have been unhelpful. The inpatient video-EEG can aid with:

- Differentiating between epileptic and non-epileptic seizures

Individuals with non-epileptic seizures are an important group and account for 20% of referrals to tertiary centres for assessment of treatment-refractory 'seizures'. To complicate matters, epilepsy and non-epileptic attack disorder can co-exist. To establish the diagnosis it may be necessary to document ictal events, both clinical and EEG, by means of long-term video-EEG. The inpatient video-EEG is viewed as the 'gold standard' investigation for the diagnosis of non-epileptic events.

- Classification of seizure type and epilepsy syndrome

Long-term video-EEG recording can aid with both classification of seizure type and epilepsy syndrome.

Three narrative reviews were consulted: one on the use of long-term video-EEG monitoring in adults[83] and two on the diagnosis of non-epileptic attack disorders (NEAD).[84,85]

Secondary evidence

AHRQ 2001[50]

Eight primary studies (4 prospective and 4 retrospective) of the role of long-term video-EEG in the diagnosis of epilepsy were reviewed in the Agency for Healthcare Research & Quality review. These are summarised below. The authors of the review concluded that inpatient video-EEG and ambulatory EEG were discretionary tests and that the evidence was inconclusive on the value of any added information.

Prospective studies:

- An Australian study reported a case series of 82 children (age 2 months – 16 years, median 6 years) who underwent inpatient EEG-video telemetry.[86] 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.[87] 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.[88]
- 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.[89]

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).[90]

- 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'.[91]
- 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.[92] 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.[93]

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

27. 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 people. [2004]

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

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.[85]

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.[84,94]

Secondary evidence

No systematic reviews were identified.

Primary evidence

One RCT and four non-randomised studies were identified.

McGonigal 2002[95]

A UK study aimed to assess the yield of recorded habitual non-epileptic seizures during outpatient video-EEG, using simple suggestion techniques based on hyperventilation and photic simulation. The study design was a randomised controlled trial of 'suggestion' versus 'no suggestion'. The setting was a tertiary centre.

The participants were 30 individuals (22 female, 8 male), aged over 16 years, with a probable clinical diagnosis of non-epileptic seizures; 15 were randomised to each group.

The main outcome measures were: yield of habitual non-epileptic seizures recorded, and requirement for additional inpatient video EEG.

Ten out of 15 individuals had habitual non-epileptic seizures with suggestion; 5/15 had non-epileptic seizures with no suggestion ($p = 0.058$; not significant); 8/9 individuals with a history of previous events in medical settings had non-epileptic seizures recorded during study. Logistic regression analysis with an interaction clause showed a significant effect of suggestion in those with a history of previous events in medical settings ($p = 0.003$). An additional inpatient video-EEG was avoided in 14 of the 30 (47%).

Bhatia 1997[96]

Another study considered the usefulness of short-term recording of video electroencephalography (VEEG) as an outpatient procedure with placebo induction and intravenous saline in cases of pseudoseizures.

Fifty cases of suspected pseudoseizures were enrolled. They were divided into 2 groups: Group 1 consisted of individuals with frank pseudoseizures; Group 2 those where diagnosis was uncertain. VEEG recording was done and 10 ml of saline used for placebo-induction. Of 50 cases, 24 (48%) were

in Group 1 and 26 (52%) in Group 2. Fifteen (15/50, 30%) had a spontaneous event during VEEG. A further 15 (15/45, 33%) had an event only on placebo induction.

Parra 1998[97]

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.

Dericioglu 1998[98]

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.

Benbadis 2000[99]

A US study described the use of a multimodality provocative technique that did not use a placebo (did not use IV saline).

Twenty one individuals with a clinical suspicion for psychogenic non-epileptic seizures were eligible to undergo an activation procedure using suggestion, hyperventilation, and photic stimulation during the study period. Of 19 inductions performed, 16 (16/19, 84%) were successful in inducing the habitual episode.

8.2.6 Does an abnormal EEG predict seizure recurrence?

29. In children, young people and adults presenting with a first unprovoked seizure, unequivocal epileptiform activity shown on EEG can be used to assess the risk of seizure recurrence. [2004]

Evidence statement

Individuals presenting with a first unprovoked seizure who have epileptiform activity on their initial EEG have an increased risk of seizure recurrence. (IIb children, III adults)

The specificity of an epileptiform EEG in predicting further seizures ranges from 0.13 to 0.99, and sensitivity from 0.20 to 0.91. (II)

Details

Secondary evidence

Four systematic reviews were identified.

Berg 1991[100]

Factors predictive of seizure recurrence following a first unprovoked seizure were explored in this systematic review of 16 studies.

All studies that reported on EEG results found there was a higher risk of recurrence associated with the presence of any abnormalities. The relative risk (abnormal/normal) ranged from 1.2 to 4.1. The pooled risk of recurrence at 2 years was 27% (95% CI 21% to 33%) with a normal EEG, 58% (95% CI 49% to 66%) with epileptiform abnormalities, and 37% (95% CI 27% to 48%) with non-epileptiform abnormalities. The relative risk associated with an abnormal EEG was 1.9 (95% CI 1.5 to 2.4) in the idiopathic group, and 1.4 (95% CI 1.0 to 1.9) in the remote symptomatic group.

Both seizure aetiology and EEG results clearly and consistently separated cases into higher and lower risk groups.

Gilbert 2000[66]

In this review, the authors aimed to quantify and analyse the value of the information from an EEG after a first unprovoked seizure in children.

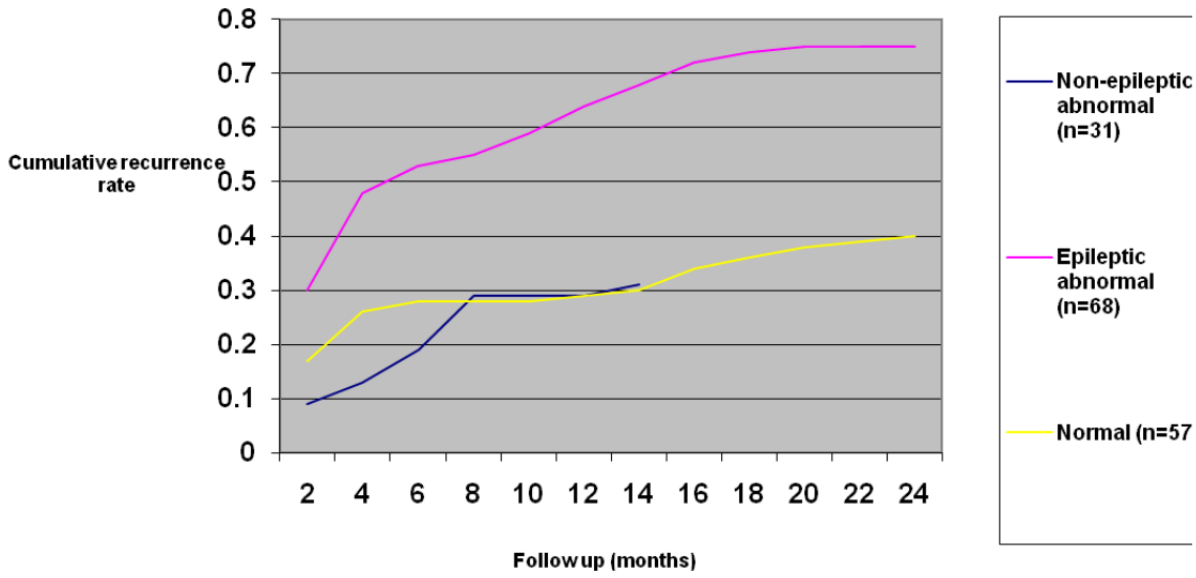
Four studies involving 831 children were included.

The pre-test probability of recurrence in all studies was found to be below the lower range of the rational testing region; that is, the expected value of the information gained from the EEG was too low to affect treatment recommendations in most children.

Hirtz 2000[72]

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.

Figure 8.1 Probability of seizure recurrence after a first unprovoked seizure as a function of the standard EEG[101] Modified with permission from Berg at al 2000



Gilbert 2003[102]

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.[102]

8.3 The role of neuroimaging in the diagnosis of epilepsy

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

31. MRI should be the imaging investigation of choice in children, young people and adults with epilepsy. [2004]

32. MRI is particularly important in those:

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

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

34. CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children and young people in whom a general anaesthetic or sedation would be required for MRI but not CT. [2004]

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

36. Children, young people and adults requiring MRI should have the test performed soon[§§§§§]. [2004]

Evidence statements

Both Magnetic Resonance Imaging (MRI) scanning and Computed Tomography (CT) scanning can identify structural abnormalities in the brain that are thought to be aetiologically relevant to a diagnosis of epilepsy. (III)

Magnetic Resonance Imaging (MRI) scanning is more sensitive and specific than Computed Tomography (CT) scanning in identifying structural abnormalities. (III)

Individuals diagnosed as having idiopathic generalised epilepsy who undergo CT and/or MRI scanning are unlikely to have any aetiologically relevant structural abnormalities. (III)

Details

This review summarises the evidence for the use of magnetic resonance imaging (MRI) and computed tomography (CT) scans in the diagnosis of epilepsy.

Both MRI and CT scans are used principally in the identification of structural abnormalities in the brain that underlie seizure disorders and thus are helpful in determining the aetiology of the disorder (axis 4 – classification).

Secondary evidence

Two systematic reviews of the literature were identified.[50,72]

AHRQ 2001[50]

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.

[§§§§§] The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.

Hirtz 2000[72]

Nine studies addressed the use of neuroimaging in children presenting with a first non-febrile seizure. The evidence consistently demonstrated that MRI was more sensitive than CT scanning. However, the studies showed that only 1.9% of images revealed clinically significant findings that contributed to treatment or management.

Primary evidence

As for evidence on EEG, the primary papers reviewed here have methodological deficiencies according to criteria for diagnostic tests.

Diagnosis of epilepsy

Berg 2000[101]

Berg and colleagues described the use of imaging in 613 children with newly diagnosed epilepsy. Data were collected prospectively over a 4 year period. Of the 613 children, 488 (79.6%) had imaging: 388 (63.3%) magnetic resonance imaging, 197 (32.1%) computed tomography scans, and 97 (15.8%) both. Half of children with idiopathic generalized epilepsy had imaging studies compared with 70% to 100% of children with other forms of epilepsy, depending on the specific type.

A summary of results is presented in Table .

Aetiologically relevant abnormalities were found in 62 (12.7% of those imaged). Fourteen of these children had otherwise completely normal presentations and histories. Their abnormalities included tuberous sclerosis (n=4), tumours (n=2), an arteriovenous malformation later diagnosed as a tumour, a cavernous angioma, cerebral malformations (n=3), and other abnormalities (n=3). Thirteen of the 14 had focal seizures and 12 had focal electroencephalographic (EEG) findings. Only one had neither.

In 18 of the 62 children with aetiologically related abnormalities, both a CT and an MRI were performed. In 15 cases, the abnormality was identified by the CT and confirmed by the MRI. In 3 cases, the CT was normal and the MRI abnormal.

Table 8-3: Frequency of neuroimaging and yield by epilepsy syndrome - Modified with permission from Berg at al 2000[101]

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) ıı	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)
Doose'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.

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

Bunn 2002[103]

One study aimed to compare the clinical benefit of CT with MRI for children investigated at a district general hospital.

A retrospective case note review of two one year periods (1992-1993 and 1996-1997) was undertaken. All children aged 18 or under who had a CT scan or MRI of the head, neck, or spine requested by a paediatrician were included.

A definitive diagnosis was made with CT in 12% of children who presented with seizures, and in 27% with MRI.

Dam 1985[104]

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).

Holt-Seitz 1999[105]

The aetiology, early mortality, predictors of prognosis, and diagnostic yields of EEG and CT scans in new-onset seizures in older people were examined in adults aged 60 or older.

Participants were identified by reviewing records of all EEG recordings undertaken in a two year period (Jan 1994 – Dec 1995) at a single hospital. 88 people with definite or probable seizure were identified, but 4 refused to participate. The initial EEG was abnormal in 61 people (73%). CT was performed in all individuals and were abnormal in 57 (68%). Only 11 individuals underwent MRI scanning and abnormalities were detected in 7, three of whom had no abnormality detected in CT.

Jallon 1997[106]

A Swiss study aimed to determine the incidence of first seizures in a population of 384,657.

In the year of study, 418 people were referred for an EEG with a first suspected epileptic seizure. After excluding 133 individuals (insufficient data, unclear diagnosis, lived outside study area), 273 participants remained.

All participants by definition had an EEG recording. 199 individuals (67%) underwent CT scanning of which 61 (32%) were normal. 56 people (19.7%) underwent MRI scanning, which was normal in 30.4%. MRI was abnormal in 16% of those with normal CT scans.

Kilpatrick 1991[107]

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 focal seizures and/or focal EEG findings as compared with 0% (0/19) of those without focal seizures.

King 1998[73]

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 focal 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 focal epilepsy. Eleven unclassified individuals with focal lesions were reclassified as having focal epilepsy. A final diagnosis of epilepsy was made in 243 (81%) of the initial group.[73]

Ramirez-Lassepas 1984[108]

The role of the CT scan in the evaluation of adults after their first seizure(s) was determined in this US study.

The hospital records of 148 individuals, aged 16 to 90 years, hospitalised for evaluation of a first acute seizure were reviewed. Included individuals had a complete neurological exam, complete metabolic workup, EEG recording, and CT scan.

Aetiology was determined in 71 participants (48%), with a structural lesion identified by CT in 55 (37%) and 16 (11%) had metabolic seizures. CT findings agreed with the results of the neurological exam in 82% of cases. CT revealed structural lesions in 14 (15%) people with non-focal findings and in 12 (22%) with generalised EEG abnormalities.

Roberts 1988[109]

A prospective study of CT scans in adults with late-onset epilepsy was set up to search for evidence of cerebrovascular disease.

The case notes of 132 consecutive new outpatients with a history of one or more epileptic seizures with age of onset 40 years or older were reviewed. Individuals were excluded if there were other neurological symptoms or there was doubt about the diagnosis. Control scans were obtained from 132 control subjects of appropriate age and sex.

15 of those with epilepsy had infarcts on CT compared with 2 of the controls (p=0.003). However, there was no difference between the groups in the presence of relevant clinical features of systemic vascular and cardiac disease. The CT evidence of cerebral atrophy was the same in both groups.

Syndromic diagnosis and classification

Atakli 1998[110]

One study aimed to identify and analyse pitfalls in the diagnosis of juvenile myoclonic epilepsy (JME). The notes of 76 individuals with well-documented diagnoses of JME (as assessed using the Panayiotopoulos diagnostic criteria) were retrospectively analysed.

All of the CT (n=33) and MRI (n=3) investigations were normal.

Harvey 1997[111]

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 focal seizures of suspected TLE origin with onset before aged 15 were recruited (Jan 1991 to Mar 1993). Of these, 63 were diagnosed with TLE. MRI was performed in 58 of the 63 (92%) children and CT in 48 of the 63 (76%). Five children did not undergo MRI because the CT was normal and their parents did not wish them to undergo MRI.

MRI revealed structural abnormalities of the temporal lobe in 24 of the 63 children (38%).

Jallon 2001[112]

One study described first unprovoked seizures and newly diagnosed epilepsies at initial presentation in a large cohort.

Individuals were referred to the study if they were older than one month, had at least one unprovoked epileptic seizure diagnosed between May 1995 and June 1996, and were likely to be followed up for at least 2 years. After exclusions (previous diagnosis of unprovoked seizures, acute symptomatic seizures, those likely to be lost to follow-up) 1,942 people were included.

One or more imaging studies were performed in 1,418 individuals (73.0%). In the first-seizure group (n=926), a neuroimaging study was performed in 78.2% of the participants (CT scan only 57.9%; MRI only 6.5%; CT scan + MRI 13.8%). This rate varied according to the epileptic syndrome: 55.0% for idiopathic localization-related, 63.5% for idiopathic generalized, 82.1% for isolated seizures, 86.0% for cryptogenic localization-related, and 88.6% for symptomatic localization-related. For those with newly-diagnosed epilepsy (n=1,016), a neuroimaging study was performed in 68.3% (CT scan only 42.9%; MRI only 12.2%; CT scan + MRI 13.2%). This rate varied according to the epileptic syndrome: 40.3% for idiopathic generalized, 60.4% for idiopathic localization-related, 65.4% for symptomatic generalized, 74.4% for cryptogenic or symptomatic generalized, 78.0% for undetermined whether focal or generalized, 78.1% for cryptogenic localization-related, and 94.2% for symptomatic localization-related.

These high rates of imaging permitted classification of seizures in 78.1% of the first-seizure group and 88.0% of the newly-diagnosed-epilepsy group; classification of syndromes in all the first seizures and 98.6% of those with newly diagnosed epilepsy; and classification of aetiology in all the first seizures and 98.8% of those with newly diagnosed epilepsy, with a reasonably high degree of certainty at the time of initial diagnosis.

Lee 2002[113]

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%.

8.4 The role of prolactin levels and other blood tests as an aid to diagnosis

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

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

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

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

Evidence statement

There is conflicting evidence as to the value of blood tests, such as serum prolactin levels, in differentiating between epileptic and non-epileptic seizures. (III)

Details

This section presents the evidence for the use of blood tests in making the diagnosis of epilepsy, and in differentiating between epilepsy and other conditions, particularly syncope. Blood tests discussed are levels of serum prolactin, neuron-specific enolase, serum creatine kinase, and white blood count.

Secondary evidence

AHRQ 2001[50]

This systematic review identified two relevant papers (Anzola[114] and Neufeld[115] 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.[49,67]

Diagnosis of epilepsy

Fein 1997[116]

The utility of serum and cerebrospinal fluid (CSF) prolactin levels was assessed in the diagnosis of children with seizures. Serum samples were analysed if the samples were taken within 90 minutes of the seizure, and CSF samples within 4 hours of the seizure. The comparison group was children who had not experienced a seizure but who otherwise required a lumbar puncture.

The positive predictive value of age-adjusted dichotomous levels (elevated and normal) of serum prolactin was 68% (95% CI 47-85%) and the negative predictive value was 76% (95% CI 61-87%).

Shah 2001[117]

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 focal seizure or a generalized seizure. Peripheral WBC count was elevated above the upper limit of normal in 36% of cases after a generalized seizure. In generalized seizures, the length of a seizure is positively associated, whereas the lapse time between the seizure onset and blood draw is negatively correlated with the increase in WBC count.

Tumani 1999[118]

The temporal profile of serial levels of neuron-specific enolase (NSE) and serum prolactin were compared in 21 individuals with single seizures. Measurements were taken at one, three, six and 24 hours after the event.

There was a significant decrease of NSE and prolactin levels over time ($p<0.001$). At one hour after the event, only 38% of individuals had increased NSE compared with abnormal prolactin levels in 81%.

Differential diagnosis between epileptic and non-epileptic attacks

Alving 1998[119]

This study aimed to evaluate the discriminative power of serum prolactin measurements in the differential diagnosis between epileptic (ES) and pseudo-epileptic seizures (PES). Blood samples were taken from 58 participants both 15 minutes after the seizure and 2 hours after the first sample.

Sensitivity for the maximal rise of serum prolactin in pseudoseizures (5.5 times baseline level) was only 20% and the negative predictive value 40%. For the cut-off in absolute level, (1025 µU/ml), the figures were 34% and 44% respectively.

Epilepsy vs syncope

Anzola 1993[114]

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%.

Lusic 1999[120]

The use of serum prolactin levels in the differential diagnosis between epileptic and syncopal attacks was examined in individuals with complex focal seizures (CPS) and individuals with vasovagal syncopal attacks (VVS)[87]. 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±305 mIU/l, VVS: 874±208 mIU/l). Elevated levels immediately after the event were found in 78% of in the CPS group, and 60% of the VVS group.[120]

Neufeld 1997[115]

The objective of this study was to determine the role of sequential serum creatine kinase (CK) levels in differentiating between generalised tonic-clonic seizures and vaso-vagal syncope in people presenting with first events of loss of consciousness. Serum levels were taken in 16 individuals on admission (i.e. within a few hours of the event) and 24-26 hours later.

Using the criteria of CK levels > 200mU/ml (3.33µkat/l) (on either admission or 24-26 hours later) and/or the elevation from the first to the second measurement of >=15mU/ml (0.25µkat/l), there were only 12% false negatives and 12% false positives.[115]

8.5 Cardiovascular tests as an aid to diagnosis

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

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

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

Evidence statement

Seizure-like attacks with a cardiovascular cause may be misdiagnosed as epilepsy. (III)

Details

This was not subject to a full evidence review for reasons given in Chapter 2.

Zaidi 2000[121]

Zaidi and colleagues conducted cardiovascular tests in 74 people with a previous diagnosis of epilepsy. Participants were included if attacks continued despite adequate AED therapy, or there was clinical uncertainty based on the seizure description. Each individual underwent a head-up tilt test and carotid sinus massage during continuous electrocardiography, electroencephalography and blood pressure monitoring.

An alternative diagnosis was made in 31 people (42%). After follow-up (10.3±6.7 months), 19 (61%) of the 31 with an alternative diagnosis were symptom free and all 31 had subjectively improved. Of the 13 people who were taking AEDs, 11 (85%) had successfully stopped AED therapy.

8.6 What is the role of neuropsychological assessment in the diagnosis and management of epilepsy?

44. Neuropsychological assessment should be considered in children, young people and adults in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory. [2004]

45. Referral for a neuropsychological assessment is indicated:

- **when a child, young person or adult with epilepsy is having educational or occupational difficulties**
- **when an MRI has identified abnormalities in cognitively important brain regions**
- **when a child, young person or adult complains of memory or other cognitive deficits and/or cognitive decline. [2004]**

Evidence statement

Neuropsychological deficits are commonly associated with epilepsy and its treatment. Awareness of these problems may facilitate education, social integration and employment. (IV)

Details

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

Narrative reviews

Two expert reviews were consulted.

Buelow 2002[122]

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.[122]

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 2001[123]

This review considered the cause and neuropathology of epilepsy, neuronal discharges, AED treatment and the associated effects on cognition and behaviour. Psychosocial factors were also discussed.

The authors concluded that a better understanding of the complex cognitive and behavioural dimensions of epilepsy would allow clinicians to provide a more holistic, person centred approach to

management. They recommended that each individual with epilepsy should be assessed individually with respect to factors unique to their seizure disorder and treatment.

9 Classification of seizures and epilepsy syndromes

9.1 Introduction

It is inadequate to simply diagnose an individual as having 'epilepsy'. Epilepsy should be viewed as a feature or symptom of an underlying neurological disorder and not as a single disease entity. It is important that specialists and generalists who treat individuals with epilepsy understand that epilepsy should be classified according to seizure type and epilepsy syndrome. The need to consider age-related epilepsy syndromes is particularly important in children with epilepsy.

It is axiomatic that the correct classification of seizure type and epilepsy syndrome should lead to the individual with epilepsy receiving appropriate investigations, appropriate treatment, and information about the likely prognosis of the seizure type and/or syndrome.

9.2 Classification of the epilepsies

46. Epileptic seizures and epilepsy syndromes in children, young people and adults should be classified using a multi-axial diagnostic scheme. The axes that should be considered are: description of seizure (ictal phenomenology); seizure type; syndrome and aetiology. [2004]

47. The seizure type(s) and epilepsy syndrome, aetiology, and co-morbidity should be determined, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment and persistence of seizures. [2004]

48. Children, young people and adults with epilepsy should be given information about their seizure type(s) and epilepsy syndrome, and the likely prognosis. [2004]

Evidence statements

The classification of epilepsy relies on evidence from expert committee reports (International League Against Epilepsy). At present the established classification system is undergoing review and current proposals have the status of 'work in progress'. (IV)

Failure to correctly classify the epilepsy syndrome can lead to inappropriate treatment and persistence of seizures. (III)

Details

Overview of classification systems

The classification of epilepsy has long been a subject of contention. The problem 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 epilepsy syndromes).[2]

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.[124] 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.[125,126] (Table 9.1, Table).

Although the ILAE 1981 and 1989 classifications remain in common use they have been the subject of criticism and debate. They have been criticised for:

- being unsatisfactory for epidemiological research[3]
- placing undue emphasis on the types of case referred to tertiary centres [127]
- placing undue emphasis on the role of the EEG at the expense of newer techniques such as MRI[3]
- not classifying epileptic seizures according to what a individual or eyewitness reports happens during a seizure (ictal semiology).[128]

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.[4] The Task Force argued that it was not possible to replace the current international classifications[125,126] 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 9.3). Epileptic seizures and epilepsy syndromes were to be described and categorised in individuals according to a system that uses standardised terminology, and that was sufficiently flexible to take into account the following practical and dynamic aspects of epilepsy diagnosis:

- Some individuals cannot be given a recognized syndromic diagnosis;
- Seizure types and syndromes change as new information is obtained;
- Complete and detailed descriptions of ictal phenomenology are not always necessary;
- 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 was also scope to simplify or expand the classification system depending on whether it was to be used by a neurologist with particular expertise in epilepsy or by a general physician or paediatrician.

A further report of the Task Force for Classification was published in 2006 with an updated list of epilepsy syndromes. Driven primarily by advances made in basic and clinical sciences over recent years, a further revision has now been proposed. Changes made essentially represent simplification of terminology. For seizures a simplified ILAE (2010) classification has been put forward (table 9.4). For the epilepsies there is no new classification as such but simplification of terminology (table 9.5). The list of syndromes remains as recognised in 2001, and updated in the 2006 Task Force report. Descriptors of aetiology have been updated, the terms idiopathic, symptomatic and cryptogenic have been replaced with genetic, structural/metabolic and unknown (table 9.6). Table 9.7 highlights key changes in terminology for ease of reference.

Table 9.1 Classification of epileptic seizures according to clinical type (1981)

1. Focal (local) seizures

1.1. *Simple focal 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 focal seizures)

1.2. *Complex focal 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. *Focal seizures evolving to secondarily generalized seizures* (may be generalized tonic-clonic, tonic, or clonic)

1.3.1. Simple focal seizures evolving to generalized seizures

1.3.2. Complex focal seizures evolving to generalized seizures

1.3.3. Simple focal seizures evolving to complex focal 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 seizures[126] **Reprinted by permission of the journal *Epilepsia***

Table 9-2: Classification of epilepsies and epileptic syndromes (1989)

1. Localization-related (focal, local,) epilepsies and syndromes
- 1.1. *Idiopathic* (listed in order of age of onset)
  - 1.1.1. Benign childhood epilepsy with centrotemporal spike
  - 1.1.2. Childhood epilepsy with occipital paroxysms
- 1.2. *Symptomatic*
- 1.3. *Cryptogenic*

2. Generalized epilepsies and syndromes
- 2.1. *Idiopathic* (listed in order of age of onset)
  - 2.1.1. Benign neonatal familial convulsions
  - 2.1.2. Benign neonatal convulsions
  - 2.1.3. Benign myoclonic epilepsy in infancy
  - 2.1.4. Childhood absence epilepsy (pyknolepsy)
  - 2.1.5. Juvenile absence epilepsy
  - 2.1.6. Juvenile myoclonic epilepsy (impulsive petit mal)
  - 2.1.7. Epilepsy with grand mal (generalized tonic-clonic) seizures on awakening
- 2.2. *Cryptogenic or symptomatic* (listed in order of age of onset)
  - 2.2.1. West syndrome (infantile spasms)
  - 2.2.2. Lennox-Gastaut syndrome
  - 2.2.3. Epilepsy with myoclonic-astatic seizures
  - 2.2.4. Epilepsy with myoclonic absences
- 2.3. *Symptomatic*
  - 2.3.1. Non-specific etiology
    - 2.3.1.1. Early myoclonic encephalopathy
    - 2.3.1.2. Early infantile epileptic encephalopathy with suppression burst
    - 2.3.1.3. Other symptomatic generalized epilepsies not defined above
  - 2.3.2. Specific syndromes
    - 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

3. Epilepsies and syndromes undetermined whether focal or generalized
- 3.1. *With both generalized and focal seizures*
  - 3.1.1. Neonatal seizures – *excluded from G/L*
  - 3.1.2. Severe myoclonic epilepsy in infancy
  - 3.1.3. Epilepsy with continuous spike-waves during slow wave sleep
  - 3.1.4. Acquired epileptic aphasia (Landau-Kleffner syndrome)
- 3.2 *Without unequivocal generalized or focal features*

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.

4 Special syndromes
- 4.2 Febrile convulsions
- 4.3 Isolated seizures or isolated status epilepticus
- **4.4** Seizures occurring only when there is an acute metabolic or toxic event

Modified from: Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes[125] **Reprinted by permission of the journal *Epilepsia***

Idiopathic: No underlying cause other than a possible hereditary predisposition.

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

Cryptogenic: A disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic, but the aetiology is not known.

Table 9-3: A proposed diagnostic scheme for people with epileptic seizures and with epilepsy (2001)

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. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: *Syndrome*, from the List of Epilepsy Syndromes, 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.
- [Axis 5: *Impairment*, this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from an impairment classification adapted from the WHO ICIDH-2.]

Modified from: Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology[4]
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Table 9-4a: Classification of seizures (2010)

Classification of seizures[a]

Generalized seizures

- Tonic–clonic (in any combination)
- Absence
  - Typical
  - Atypical
  - Absence with special features
    - Myoclonic absence
    - Eyelid myoclonia
- Myoclonic
  - Myoclonic
  - Myoclonic atonic
  - Myoclonic tonic
- Clonic
- Tonic
- Atonic

Focal seizures

Unknown

-Epileptic spasms

[a] Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.

From: Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer I. (2010) Revised terminology and concepts for organisation of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology 2005-2009. *Epilepsia;*51:676-685

Table 9-4b: Descriptors of focal seizures according to degree of impairment during seizure (2010)

Descriptors of focal seizures according to degree of impairment during seizure[a]
According to severity • Without impairment of consciousness or awareness • With observable motor or autonomic components • Involving subjective sensory or psychic phenomena only. With impairment of consciousness or awareness. • Evolving to a bilateral, convulsive [b] seizure (involving tonic, clonic, or tonic and clonic components). *According to putative site of origin* *According to elemental sequence of clinical features*
[a]For more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001.

Modified from: Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer I. (2010) Revised terminology and concepts for organisation of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology 2005-2009. *Epilepsia;*51:676-685

Table 9-5: Electroclinical syndromes and other epilepsies (2010)

Electroclinical syndromes and other Epilepsies
Electroclinical syndromes arranged by age at onset [a]
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders

Childhood

Febrile seizures plus (FS+) (can start in infancy)

Panayiotopoulos syndrome

Epilepsy with myoclonic atonic (previously astatic) seizures

Benign epilepsy with centrotemporal spikes (BECTS)

Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)

Late onset childhood occipital epilepsy (Gastaut type)

Epilepsy with myoclonic absences

Lennox-Gastaut syndrome

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]

Landau-Kleffner syndrome (LKS)

Childhood absence epilepsy (CAE)

Adolescence – Adult

Juvenile absence epilepsy (JAE)

Juvenile myoclonic epilepsy (JME)

Epilepsy with generalized tonic–clonic seizures alone

Progressive myoclonus epilepsies (PME)

Autosomal dominant epilepsy with auditory features (ADEAF)

Other familial temporal lobe epilepsies

Less specific age relationship

Familial focal epilepsy with variable foci (childhood to adult)

Reflex epilepsies

Distinctive constellations

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)

Rasmussen syndrome

Gelastic seizures with hypothalamic hamartoma

Hemiconvulsion–hemiplegia–epilepsy

Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known

structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)

Epilepsies attributed to and organized by structural-metabolic causes

Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)

Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)

Tumor

Infection

Trauma

Angioma

Perinatal insults

Stroke

Etc.

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se

Benign neonatal seizures (BNS)

Febrile seizures (FS)

[a]The arrangement of electroclinical syndromes does not reflect aetiology.

[b]Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

From: Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer I. (2010) Revised terminology and concepts for organisation of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology 2005-2009. *Epilepsia;*51:676-685

Table 9-6: Underlying type or cause (aetiology) (2010)

Underlying type of cause (aetiology) (taken from Berg et al 2010)
1. **Genetic:** The concept of genetic epilepsy is that *the epilepsy is, as best understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (eg SCN1A and Dravet syndrome) or the evidence for a central role of a genetic component may come from appropriately designed family studies.* Designation of the fundamental nature of the disorder as genetic does *not* exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease. At the present time there is virtually no knowledge to support specific environmental

influences as causes of or contributors to these forms of epilepsy
2. **Structural/metabolic**: Conceptually, there is *a distinct other structural or metabolic condition or disease* that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (eg tuberous sclerosis, many malformations of cortical development); however, *as we currently understand it*, there is a separate disorder interposed between the genetic defect and the epilepsy
3. **'Unknown cause'**: Unknown is meant to be viewed neutrally and to designate that *the nature of the underlying cause is as yet unknown*; it may have a fundamental genetic defect at its core or it may be the consequence of a separate as yet unrecognised disorder

From: Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer I. (2010) Revised terminology and concepts for organisation of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology 2005-2009. *Epilepsia;*51:676-685

Table 9-7: Major changes in terminology and concepts for classification of the epilepsies and seizures

Old term and concept	New term and concept
Aetiology	
Idiopathic: presumed genetic Symptomatic: secondary to a known or presumed disorder of the brain Cryptogenic: presumed symptomatic	Genetic: genetic defect directly contributes to the epilepsy,and seizures are the core symptom of the disorder Structural–metabolic: caused by a structural or metabolic insult or disorder of the brain Of unknown cause: the cause is unknown and might be genetic, structural, or metabolic
Seizures	
Generalised: first changes indicate initial involvement of both hemispheres Focal: first changes indicate activation of a system of neurons limited to part of one cerebral hemisphere Spasms were not acknowledged Complex, simple partial, secondarily generalised	Generalised: arising within and rapidly engaging bilaterally distributed networks Focal: originating within networks limited to one hemisphere Addition of epileptic spasms; grouped as unknown owing to insufficient evidence to classify as focal, generalised, or both Earlier term abandoned in favour of precise descriptionof focal seizures according to ictal semiology
Epilepsies	

Generalised: epilepsies with generalised seizures	Earlier term abandoned
Focal: epilepsies with focal seizures	Earlier term abandoned
Major changes in terminology and concepts for classifi cation of the epilepsies and seizures: Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classifi cation and Terminology, 2005-2009. *Epilepsia* 2010; published online Feb 26. DOI:10.1111/j.1528-1167.2010.02522.x.	

From: Berg AT, Cross JH. Towards a modern classification of the epilepsies (2010) Lancet Neurology. 9(5):459-461

9.3 What is the role of classification in adults and children with epilepsy?

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

The example presented below shows the importance of correct diagnosis and classification in juvenile myoclonic epilepsy (JME).

Delgado-Escueta 1984[129]

In one study, 43 individuals, aged 15 to 69 years, were referred for uncontrolled convulsive seizures. After the diagnosis of JME was established, 86% were either seizure-free or satisfactorily controlled on valproate alone, or with other AEDs.

Grunewald 1992[130]

In a London-based case series, 15 definite cases of JME were identified from 180 consecutive referrals to an epilepsy clinic. Diagnoses on referral were usually vague and non-syndromic. In many cases, the syndromic features were accurately recorded in the notes, but the referring physician appeared to be unaware of JME and a correct diagnosis not made. Following the diagnosis of JME and optimisation of drug treatments, myoclonic jerks improved or disappeared in 13 of the 15 individuals. The authors suggested that a syndromic classification should be recorded for all people with epilepsy, and this should be regularly reviewed particularly if seizures are poorly controlled.

Montalenti 2001[131]

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 focal epilepsy, or were not classified (n=33). The most frequent reason for misdiagnosis was an underestimation or misinterpretation of myoclonic jerks by both the individual or the referring physician, suggesting that the correct diagnosis is dependent on the knowledge of the physician.

This has also been identified in other studies.[130,132] 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.[133,134]

10 Pharmacological treatment of epilepsy

10.1 Introduction

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) taken daily to prevent the recurrence of epileptic seizures. It is important that the treatment strategy and suitability of the AED is determined by the prescriber, in collaboration with the individual with epilepsy and/or carer, before drug therapy is commenced. Factors determining suitability include: type of seizure and/or epilepsy syndrome; childbearing potential; the presence of co-morbidity; individual and/or carer preferences; the presence of contraindications to the drug; potential interactions with other drugs; potential adverse effects and the licensed indication of the drug.

The first 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.

The next chapter 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 2009 Pharmaceutical Price Regulation Scheme (PPRS) stated that subject to discussion with affected parties, the Department of Health (DH) would introduce generic substitution in primary care. Generic substitution would enable pharmacists and other dispensers to fulfil a prescription for a branded medicine by dispensing an equivalent generic medicine. A public consultation on the proposals to implement generic substitution took place from 5 January to 30 March 2010. Three main responses were yielded:

- *There is a strongly held perception by respondents that generic substitution posed a threat to patient safety. If the proposals were to be implemented, these concerns would arise in the frontline delivery of NHS services, impacting on the workload of health care professionals.*
- *The position on the cost-effectiveness of generic substitution implementation is inconclusive. There is a strong sense that the effort involved in implementing a formal generic substitution scheme was simply too great for the potential gain.*
- *Other, less nationally prescriptive mechanisms for further supporting the use of generic medicines can be explored.*

In the light of the public consultation findings, the DH will not be progressing any further the implementation of generic substitution. Instead the DH will be looking at further ways to support the use of generic medicines in a way that is acceptable to patients, recognising that there are still some savings that can potentially be delivered in this area. [******]

Therefore, for the purposes of this guideline update, the GDG considered it acceptable to review the evidence related to clinical and cost-effectiveness of specific drug therapy and make recommendations accordingly

[******] http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_120433.pdf

Pharmacological treatment of epilepsy

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

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

10.2 How many times should monotherapy be tried before combination therapy is considered?

51. It is recommended that children, young people and adults should be treated with a single AED (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period. [2004]

52. 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 child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. [2004]

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

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

Evidence statements

There is no evidence to show whether alternative substitution or add-on therapy is more effective as a treatment strategy. (III)

Evidence for combination therapy with the newer antiepileptic drugs showed that a significant proportion of adults and children who do not achieve seizure freedom on monotherapy could derive worthwhile benefit from combination therapy. Expert opinion suggested that before combination therapy is considered, adults and children should be given a trial of all appropriate monotherapy regimens, and that caution is needed during changeover periods between drugs. (Ia NICE)

Details

No systematic reviews of RCTs were identified. One RCT was identified that compared alternative monotherapy with combination therapy in individuals with recently diagnosed epilepsy.[135] However, participants may have tried several monotherapy regimes before inclusion, so this RCT was excluded. No other RCTs were identified.

Other evidence

Kwan 2000[136]

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 2003[137]

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.[137] 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.[137]

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

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

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

57. AED therapy should be considered and discussed with children, young people and adults and their family and/or carers as appropriate after a first unprovoked seizure if:

- **the child, young person or adult has a neurological deficit**
- **the EEG shows unequivocal epileptic activity**
- **the child, young person or adult and/or their family and/or carers consider the risk of having a further seizure unacceptable**
- **brain imaging shows a structural abnormality. [2004]**

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

Evidence statements

In adults and children who present with a first unprovoked seizure the risk of recurrence varies widely. (IIb)

Factors which are associated with an increased risk of recurrence include:

- *presence of neurological abnormalities*
- *epileptiform abnormalities on EEG*

- *seizure type and/ or epilepsy syndrome. (IIb)*

Treatment of a first unprovoked seizure reduces the risk of recurrence in the short-term. (Ia children, Ib adults)

In children, treatment of a first unprovoked seizure does not alter the long-term prognosis for seizure remission. (Ia)

10.2.1.1 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 1991[100]

A systematic review of the risk of seizure recurrence following a first unprovoked seizure was undertaken by Berg & Shinnar in 1991. Their literature review reviewed all relevant studies up to 1990. The authors conducted a meta-analysis of 16 studies and found that three methodological factors explained much of the reported variation:

- study inclusion criteria (whether participants were enrolled at the time of their first seizure or if those with prior seizures were included);
- retrospective versus prospective ascertainment of participants;
- the interval between the first seizure and time at which risk was assessed.

Overall risk of recurrence

From the 16 studies reviewed the overall pooled estimate of risk of recurrence was 51% (95% CI 49% to 53%). To allow for comparable results the risk of recurrence at two years was calculated. The risk was 36% (95% CI 32% to 39%) in the prospective first seizure studies reviewed and 43% (95% CI 40% to 47%) in the retrospective first seizure studies reviewed.

Factors predictive of risk of recurrence

Aetiology (Neurological abnormality) - All reviewed studies found increases in risk of recurrence associated with abnormal neurological status (congenital and acquired neurological deficits) with a pooled relative risk of 1.8 (95% CI 1.5 to 2.1).

EEG - Children (3 studies reviewed) with epileptiform abnormalities on EEG are more likely to have a recurrence than children with normal EEGs (pooled RR 2.0, 95% CI 1.6 to 2.6).

Aetiology and EEG - Three studies provided information about risk of recurrence as a function of aetiology and EEG together. The risk was lowest in the cryptogenic group who had normal EEGs (24%, 95% CI 19% to 29%) and highest in the group with abnormal neurological status and an abnormal EEG (65%, 95% CI 55% to 76%).

Hirtz 2003[138]

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.[138]

Are there factors that increase the risk of recurrence?

The authors cited the findings of the Berg & Shinnar review[100] that the underlying aetiology and whether the EEG is normal or abnormal were consistently related to the risk of recurrence.[138]

Primary evidence

Hart 1990[139]

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 focal or complex focal seizures (94%, 95% CI 90% to 99%, by 36 months) than for those with generalised tonic clonic seizures (72%, 95% CI 67% to 77%, by 36 months).

Macdonald 2000[10]

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]

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

Secondary evidence

Berg 1991[100]

A systematic review of the risk of seizure recurrence following a first unprovoked seizure was undertaken by Berg & Shinnar in 1991. Their literature review reviewed all relevant studies up to 1990. The authors identified one RCT[140] in which treatment of a first seizure was associated with a significant reduction in risk of recurrence.

Hirtz 2003[138]

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.[140] 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.[140]

In studies involving both children and adults, outcome was not provided based on age. One study[141] 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.[141]

However, these results were not found in another randomised study[142] (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 [142,143].

One study [142] had 419 subjects, of whom 114 were between 2 and 16 years of age. This study compared the probability of experiencing a remission, that is, 1 or 2 seizure-free years, in those

treated after a first seizure versus in people treated after a second seizure. Follow-up was for at least 3 years or a minimum of 2 years seizure-free. Individuals treated after the first seizure and those treated after a second seizure had the same probability of achieving a 1- or 2-year seizure remission (68%, n=215 versus 60%, n=204) (relative risk 1.04, 95% CI 0.82 to 1.30).

Another smaller study [143] 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.[138]

10.2.2 Who should start AED treatment in adults and children?

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

60. AED therapy in children and young people should be initiated by a specialist. [2004]

61. 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 child, young person or adult and their family and/or carers as appropriate. [2004]

Evidence statement

No evidence was identified.

Details

No evidence that specifically addressed the question as to 'Who should initiate treatment?' was found. The evidence on rates and consequences of misdiagnosis reviewed in section 7 was considered by the GDG and formed the basis for the GPPs above.

10.2.3 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?

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

63. If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow. [2004]

64. The needs of the child, young person or adult and their family and/or carers as appropriate should be taken into account when healthcare professionals take on the responsibility of continuing prescribing. [2004]

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

A key issue here is the general issue of who should prescribe medication when the AED may be unlicensed for a particular clinical indication.

Evidence statement

No evidence was identified on who should continue to prescribe AED treatment.

Details

No systematic reviews or RCTs were identified.

Consensus statements

No consensus statements from professional bodies were identified that described which healthcare professional should prescribe continuing AED treatment.

10.2.4 What is the role of monitoring in adults and children with epilepsy?

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

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

68. Examples of blood tests include:

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

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

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

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

Evidence statements

Routine monitoring of AED blood levels does not lead to improved seizure control for people with epilepsy. (Ib)

There is no good quality evidence that shows routine monitoring of side effects leads to better health outcomes for individuals. (IV)

There is no evidence that shows routine monitoring of drug usage leads to better health outcomes for individuals. (IV)

[††††††] Please note that 'valproate' has been changed to 'sodium valproate' to be consistent with the terminology used in this update.

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?

10.2.4.1 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 2001[50]

This systematic review on the management of people with newly diagnosed epilepsy reviewed 24 prospective interventional studies that had a monitoring component. None of these studies had as a primary objective the testing of monitoring interventions necessary for optimal care but in nearly all, this was a monitoring intervention dictated by a research study protocol and not optimal care. Therefore, the review was excluded.

Swedish Council on Technology Assessment in Healthcare 1998[144]

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.[144]

Primary evidence

Jannuzzi 2000[145]

This RCT assessed the clinical impact of monitoring serum concentrations of antiepileptic drugs (AEDs) in individuals with newly diagnosed epilepsy. 180 people with focal 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.

Froscher 1981[146]

To evaluate whether knowledge of plasma levels of antiepileptic drugs has an effect on therapeutic outcome, 127 people with epilepsy were randomly assigned to two groups (A and B). Plasma levels of group A were reported to the treating physician who attempted to keep the plasma levels within the 'therapeutic range'. The treating physician was not informed of the results of plasma level determinations of group B. Data from 105 participants were available for assessment at the end of the study year.

Seizure control improved to a similar degree in both groups. Therapeutic results of groups A and B were not significantly different. The reduction in seizure frequency was associated with an increase in plasma concentrations of the antiepileptic drugs. The proportion of individuals with serum AED levels outside the optimal range did not change substantially. The authors suggested that the physicians did not use the information correctly. They therefore concluded that, under the conditions of the study, knowledge of plasma levels of antiepileptic drugs did not improve therapeutic results.

10.2.4.2 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 1997[147]

A search for published papers on carbamazepine and valproate monotherapy (1991–1995) identified 7 relevant papers. Details of the frequency of adverse events associated with carbamazepine or valproate monotherapy were also extracted from a clinic database. The methods of detection for different adverse events were compared across the included trials and the database information. Methods included self-reporting, physical examination, laboratory investigations, adverse event checklists, specific toxicity scales, and neuropsychological testing.

For certain adverse events (diplopia, dysarthria, affect and mood disturbances, headache, dizziness, GI disturbances, dermatological disturbances, and idiosyncratic reactions) there was no difference in how the adverse events were detected. But sedation, cognitive impairments, sexual dysfunction, hair changes, nystagmus, gait disturbances, tremor, and weight change were reported more frequently when routinely checked.

This review did not link the detection of side effects with clinical outcomes. However, it is obvious that if an individual is experiencing adverse events their quality of life may be affected, and that particularly for serious adverse events such as toxicity, monitoring may be useful.

Primary evidence

No RCTs were identified.

Position statements

In 1993, the ILAE Commission on Antiepileptic Drugs published guidelines for therapeutic monitoring of AEDs. They highlighted three areas of concern:

a) The lack of strict correlation between efficacy and/or toxicity of AEDs and their blood levels for individuals.

b) Blood levels judged on an individual sampling may be misleading where there exists wide diurnal variation.

c) Accuracy of measurements must be considered.

In conclusion, the Commission recommended that

- Indiscriminate use of blood level determinations is not recommended.
- The use of blood levels to adjust dosage so that levels fall within the defined 'therapeutic range' is a waste of time and money, and may even be dangerous.
- A target range is better developed for each individual based on the severity of the epilepsy and tolerance of side effects.

A list of situations where blood levels may be useful was presented. This included routine determinations for all individuals based on theoretical grounds only, tailored determinations with specific purposes (for example, when an individual complains of toxic signs that may be dose related, or in specific physiologic states such as pregnancy), and those where blood levels should never be used.[148]

10.2.4.3 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.

10.2.5 What influences AED treatment concordance in adults and children?

72. Adherence to treatment can be optimised with the following:

- **educating children, young people and adults and their families and/or carers in the understanding of their condition and the rationale of treatment**
- **reducing the stigma associated with the condition (see also section 18.5)**
- **using simple medication regimens**
- **positive relationships between healthcare professionals, the child, young person or adult with epilepsy, and their family and/or carers. [2004]**

73. 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 children, young people and adults with epilepsy, including school staff, social care professionals and others. [2004]

Evidence statements

Adherence to treatment is associated with many factors. (III)

No evidence on factors associated with other aspects of concordance was identified. (III)

Details

Methodological issues

Concordance refers to a consultation process between a healthcare professional and an individual. Compliance or adherence refers to a specific behaviour: was the medicine taken in accordance with the wishes of the healthcare professional?[149] '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.[150]

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.[151]

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

Table 10-28: Factors affecting adherence to medication regimens in people with epilepsy[151]

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.

10.2.6 When and how should AED treatment be discontinued in adults and children?

74. The risks and benefits of continuing or withdrawing AED therapy should be discussed with children, young people and adults, and their families and/or carers as appropriate, who have been seizure free for at least 2 years (see Appendix H[‡‡‡‡‡‡]). [2004]

[‡‡‡‡‡‡] Appendix H provides tables for the prognosis for remission of seizures in adults.

75. The decision to continue or withdraw medication should be taken by the child, young person or adult, 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 children, young people and adults, and their family and/or carers as appropriate, should understand their risk of seizure recurrence on and off treatment. This discussion should take into account details of the child, young person or adult's epilepsy syndrome, prognosis and lifestyle. [2004]

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

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

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

Evidence statements

Characteristics that predict a decreased risk of recurrence of seizures after AED withdrawal in adults with epilepsy are the:

- duration of seizure freedom before withdrawal (Ib)

Characteristics that predict an increased risk of recurrence of seizures after AED withdrawal in adults with epilepsy are:

- history of focal seizures
- history of myoclonic seizures
- history of tonic-clonic seizures
- seizures after commencement of AED treatment
- on more than one AED (Ib)

Characteristics that predict a decreased risk of recurrence of seizures after AED withdrawal in children with epilepsy are:

- period seizure free (2 years or more) (Ia)

Characteristics that predict an increased risk of recurrence of seizures after AED withdrawal in children with epilepsy are:

- history of focal seizures
- epileptiform abnormalities on EEG (Ia)
- presence of learning disabilities (Ib)

There is no good quality evidence (see Evidence Tables in Appendix F for methodological issues) that tapering AED medication at different rates has a difference on outcomes for people with epilepsy. (Ib children, no evidence for adults)

10.2.6.1 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 1994[152]

A systematic review was undertaken to determine the risk of relapse at 1 and 2 years after discontinuation of antiepileptic medication and to examine the strength of association between the risk of relapse and three commonly assessed clinical factors:

- age of onset of epilepsy
- presence of an underlying neurologic condition
- and an abnormal EEG.

The authors used explicit strategies to identify papers, select studies and extract data.

Forty two studies were identified, of which 25 met their inclusion criteria. Data on 5354 individuals were included. The proportion of those who relapsed ranged from 12% to 67%. Overall, the risk of relapse at 1 year was 0.25 (95% CI, 0.21 to 0.30) and at 2 years it was 0.29 (95% CI, 0.24 to 0.34). Relative to epilepsy of childhood onset, epilepsy of adolescent onset was associated with a relative risk of relapse of 1.79 (95% CI, 1.46 to 2.19). Compared with childhood-onset epilepsy, adult-onset epilepsy was associated with a relative risk of 1.34 (95% CI, 1.00 to 1.81). Individuals with remote symptomatic seizures were more likely to relapse than those with idiopathic seizures; the relative risk was 1.55 (95% CI, 1.21 to 1.98). An abnormal EEG was associated with a relative risk of 1.45 (95% CI, 1.18 to 1.79).

Quality Standards Subcommittee of the American Academy of Neurology 1996[153]

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, 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 focal or generalized seizure;
- normal neurological examination and normal I.Q.;
- EEG normalized with treatment.[153]

Sirven 2003[154]

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 focal 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 focal 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.[154]

Primary evidence (adults)

MRC AED withdrawal study group 1991[155]

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, phenobarbital, 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).

Table 10-29: Influence of individual characteristics on seizure recurrence[155]

Factor	**Relative risk (95% CI) (multivariate model)**
History of focal 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.

MRC AED withdrawal study group 1993[156]

The aim of this study was to develop and test a prognostic index for the recurrence of seizures after a minimum remission of seizures of two years in people with a history of epilepsy. This study used data from the RCT reported above[155] 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 secondarily 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.[156]

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 10.30 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.[157]

Table 10-30: Prognostic index for recurrence of seizures within one and two years after continuing AED treatment or starting slow withdrawal

Adapted from MRC AED Drug Withdrawal Group 1993[156] 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	$1-0.60^{z}$

10.2.6.2 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 1994[158]

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.[158]

10.2.7 In adults/children with epilepsy on AEDs does management of drug withdrawal by a generalist as opposed to a specialist lead to different outcomes?

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

Evidence statement

No evidence was identified.

Secondary evidence

No systematic reviews were identified.

Primary evidence

No RCTs were identified.

Other evidence

There was no specific evidence reviewed on the discontinuation of therapy by either specialist or generalist.

10.2.8 New recommendations and link to evidence

Recommendation	**80. When possible, choose which AED to offer on the basis of the presenting epilepsy syndrome. If the epilepsy syndrome is not clear at presentation, base the decision on the presenting seizure type(s). [new 2012]**
Relative values of different outcomes	Good practice suggests optimal management involves appropriate AED for syndrome diagnosis.
Trade off between clinical benefits and harms	Several syndromes may present with multiple seizure types, and therefore individuals are at risk of seizure exacerbation with certain AEDs if this is not taken into consideration. At diagnosis it is recognised that epilepsy syndrome may be unclear; choice may then need to be made on the basis of seizure type, taking into consideration most likely epilepsy syndrome according to age.
Economic considerations	Incorrect management of certain epilepsy syndromes leads to suboptimal seizure control and possible cognitive impact, which in turn result in greater morbidity in the long term and greater burden on NHS health services. The GDG recognised that it is essential to initiate treatment in order to gain seizure control and that in the absence of a clear syndromic diagnosis, it is reasonable to prescribe cost-effective AEDs on the basis of presenting seizure type(s).
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	No other considerations

Recommendation	**81. Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person or adult, considers that this is not a concern. In the case of a child or young person this discussion may involve the parent or carer as well. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and 'British national formulary' (BNF; available at http://bnf.org.uk) on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations. [new 2012]♣§§§§§§**
Relative values of different outcomes	The 2004 recommendation in this area stated: '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' Stakeholder responses to consultation on this update indicated that the 2004 recommendation in this area was the focus of much debate in practice as it was never the subject of formal evidence review and labelled as a good practice point in 2004. Although still not subject to formal evidence review in this update, good clinical practice suggests that bioavailability should remain constant where possible. This is consistently endorsed by patient groups as it is a very real issue that causes both patients and epilepsy charities concern.
Trade off between clinical benefits and harms	Abrupt changes in AED levels within the blood can lead to loss of previously gained seizure control, or in extreme circumstances status epilepticus. Maintenance of constant levels where possible minimises the risk to the individual. The clinician and patient representatives of the GDG felt that an efficient and cost-effective use of healthcare resources meant more than prescribing the cheapest version of a drug. A single seizure, in addition to being potentially life-threatening, has enormous effects on an individual in terms of a potential impact on daily life through loss of driving licence or employment or both. Management of further seizures results in increased healthcare costs, with more appointments, investigations and admissions.

♣ Recommendations 1, 182, 184, 191 and 283 describe the principles of decision making and best practice in relation to effective and appropriate consultation between healthcare professionals and children, young people and adults with epilepsy.

§§§§§§ In November 2013, the MHRA issued new advice about oral anti-epileptic drugs (AEDs) and switching between different manufacturers' products of a particular drug. Following a review of the available evidence, the Commission on Human Medicines (CHM) has classified AEDs into 3 categories depending on the level of potential concerns related to switching between different manufacturers' products. Consult the MHRA advice for more information.

	The GDG members were all aware of examples of people changing brands with subsequent relapse in their seizures. They also recognised that stress associated with change (not just in medication) can make people vulnerable to seizures.
Economic considerations	It is recognised that abrupt changes in bioavailability can lead to serious consequences affecting NHS resource use for example hospital admission for increased seizures, increased access to other NHS services and consequent impact on aspects of quality of life. It was also noted that generic substitution does not necessarily translate to cost savings given that some generically produced drugs have higher unit costs than their brand name equivalent. The Department of Health consultation exercise on generic prescribing in 2009 considered these issues and in consequence, did not proceed with pharmacy led generic substitutions. The GDG also noted that this remains a contentious issue across a number of clinical specialties and are aware of continued discussions between clinical experts and the Medicines and Healthcare Regulatory Agency (MHRA) in attempts to resolve this issue from a clinical and cost effectiveness perspective.
Quality of evidence	The original 2004 recommendation was developed by GDG consensus. After representation by user groups to DoH in 2009, there was acceptance that epilepsy was different to other conditions and that there was much less margin for error, in view of the possible serious consequences that may result from a change in bioavailability. Within the field, it is argued that not all AEDs have a narrow therapeutic index and/or low solubility. There is a wide spectrum of AEDs with different pharmacokinetic profiles, therapeutic indexes and physiochemical properties which might have an impact on bioavailability which does not necessarily support a blanket recommendation against changing formulation or brand of AED. Nevertheless, the GDG consensus was that this detailed knowledge for a particular AED should always impact on prescribing decisions before switching the formulation or brand of AED. Communication with the MHRA indicates that there is not currently a full review of data on many AEDs to enable a valid evidence based position across the board in this area. The GDG are aware that some publications in this area have indicated that there are concerns that the bioequivalence studies undertaken as part of the licensing process for generic antiepileptic drugs may not be large enough or in the right population to show the full range of possible bioavailabilities, and that the bioavailability limits allowed by regulatory authorities are too wide for application in epilepsy. Regulatory authorities do not require the bioavailability of new generic preparations to be compared

	with existing generic preparations. In theory, therefore, there could be a greater variability between the bioavailability of different generic preparations than between a brand and a generic. The GDG are aware of further evidence in this area but recognise that they have been unable to review it formally within the scope of this update review and are therefore unable to make a more definitive recommendation.
Other considerations	The GDG felt strongly that in the absence of a formal evidence review it should remain the case that the best practice is to maintain consistency of supply of an AED preparation/manufacturer and the prescriber needs to consider carefully in partnership with the individual (and families or carers as appropriate) whether it is safe or acceptable for an individual patient to switch between brands and therefore changed the focus of the original 2004 recommendation to this end. In revising this recommendation in this way, the GDG felt the following issues were important to note here. Feedback from the GDG pharmacist representative endorsed the position that there are risks to switching modified release preparations with normal release preparations and in switching from one modified release preparation to another modified release preparation as releasing profiles are not necessarily the same. Historically, there has been a tendency to avoid switching phenytoin, as some time ago, a company changed the excipient causing an outbreak of overdose and many patients ended up in hospital due to toxicity. However, the GDG recognise the modern licensing system is sufficient to prevent this problem from occurring It was also noted that most normal release preparations can be switched to another normal release preparations because bioavailability studies have been conducted prior to the licensing. The GDG felt it was important to advise prescribers to refer to the SPC and BNF, but wished to make it clear that these sources do not give comprehensive advice on the safety or otherwise of switching between brands of AEDs. It was also felt important to provide tailored information to mitigate against any concern that less well informed patients may be encouraged to change to generics inappropriately. The specific needs of children, individuals with learning disabilities, as well as elderly people who take many medications, should be considered in discussions between prescribing healthcare professionals and children, young people and adults with epilepsy. The GDG also felt it important for prescribing healthcare professionals to always consider the principles of engaging individuals in making decisions about their care and therefore felt it appropriate to highlight recommendations made earlier in this guideline that endorse this

	position in a footnote to this recommendation. The GDG noted that changes in metabolic functions in older people are also perhaps more sensitive to side effects which may have less noticeable impact in younger people, especially those which affect balance with consequent problems. Breakthrough seizures may also be less obvious to an observer in this group. The GDG felt that organisational structures related to medicines management, such as medicines management committees, should also carefully consider these issues when making local decisions.

Recommendation	**82. If using carbamazepine, offer controlled-release carbamazepine preparations. [new 2012]**
Relative values of different outcomes	The GDG felt that reduction of adverse effects and efficacy at reducing seizures were important outcomes for this recommendation.
Trade off between clinical benefits and harms	Carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations. A Cochrane review (Powell 2010) looked at immediate-release versus controlled-release carbamazepine and found 10 randomised controlled trials. There were conflicting results as to whether controlled-release or immediate-release carbamazepine had an advantage for reduction in seizure frequency. However, six out of nine of the trials found a trend towards a less favourable side effects profile for immediate-release carbamazepine compared to controlled-release, four of these were statistically significant. The GDG's opinion was that controlled-release is preferable to immediate-release as it avoids high peak concentrations.
Economic considerations	Original economic modelling undertaken for the guideline showed that controlled-release carbamazepine was more cost-effective than immediate-release carbamazepine. In the decision model, they were assumed to be equally efficacious and controlled-release carbamazepine was shown to have a slightly lower risk of withdrawal due to adverse events. Based on this assumption, hypothetical patients taking controlled-release carbamazepine consistently experienced more QALYs than those taking immediate-release. The rank of the different preparations in terms of cost is sensitive to the unit costs used. The weighted average unit cost per milligram for immediate-release carbamazepine is higher than the weighted average unit cost per milligram for controlled-release carbamazepine. This is largely driven by the price of non-proprietary normal release carbamazepine which is more costly than brand name Tegretol. Normal release Tegretol is less costly than non-proprietary controlled-release carbamazepine. In a sensitivity analysis where the cost of Tegretol was used, controlled-release carbamazepine was still very likely to represent good value for money. Costing listed in the BNF and NHS Drug Tariff indicate that controlled-release non-proprietary carbamazepine and controlled-release Tegretol and controlled-release Carbagen (another brand name carbamazepine product) are very similar in cost. In terms of the different formulations' effect on compliance and side effects, the benefits of the controlled-release preparation are likely to be worth a difference in cost. It appears to be better tolerated and may therefore improve adherence.
Quality of evidence	The recommendation was based upon the consensus opinion of

	the GDG. The GDG consulted evidence from a Cochrane systematic review. The Cochrane review included randomised controlled trials withlimitations. They were small trials and only one of the studies reported randomisation. None of the studies had details of allocation concealment.
Other considerations	No other considerations.

Recommendation	**83. When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. [new 2012]**
Relative values of different outcomes	The GDG placed most importance on the incidence of major malformations, miscarriages and neurodevelopmental outcomes for the child of a mother with epilepsy.
Trade off between clinical benefits and harms	The risk of harm to the mother and unborn child from seizures needs to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity of any drug, including sodium valproate, into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. Drugs and doses that may be cost-effective in the general epilepsy population, such as sodium valproate, may not be as cost-effective in this group due to its potential teratogenic effect.
Quality of evidence	Evidence comes from three systematic reviews; one review focused on incidence of malformation and the other two on child neurodevelopmental outcomes. No individual RCTs were reviewed. One observational cohort study [159] that was published after the guideline update search cut-off was also identified. This study did not meet the inclusion criteria for the evidence review, but was considered by the GDG as corroborative evidence to inform this recommendation particularly the dose-dependent risk with sodium valproate. This recommendation was also based on GDG consensus opinion.
Other considerations	This recommendation was updated from the first edition of this guideline (2004).

Recommendation	**84. Maintain a high level of vigilance for treatment-emergent adverse effects (for example, bone health issues and neuropsychiatric issues)[*******] [new 2012]**
Relative values of different outcomes	The GDG felt that the appearance of severe adverse effects should be closely monitored.
Trade off between clinical benefits and harms	The evidence available reported short-term outcomes. We specifically looked at adverse effects which were in 10% or more of the treatment arms so it was unlikely to highlight severe long-term adverse events. It was the GDG consensus that there can be a higher risk of bone health issues such as osteopenia and osteoporosis in patients taking certain drugs such as carbamazepine, phenobarbitone, phenytoin, primidone and sodium valproate due to a decrease in bone mineral density associated with these AEDs. There is a small risk associated with carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide for suicidal thoughts and behaviour.
Economic considerations	There was no economic evidence specifically addressing the impact of adverse events on the cost effectiveness of drugs used in the treatment of individuals with epilepsy. However, serious adverse events (short and long term) can affect an individual's quality of life and lead to increased costs to the NHS. Heightened awareness of these potential adverse events should ensure that a patient's treatment is altered or adjusted to reduce decrements to utility and minimise the cost of extra healthcare visits whilst maintaining seizure control.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	No other considerations.

[*******] Treatment with AEDs is associated with a small risk of suicidal thoughts and behaviour; available data suggest that the increased risk applies to all AEDs and may be seen as early as 1 week after starting treatment. Available from www.mhra.gov.uk/PrintPreview/DefaultSplashPP/CON019574?DynamicListQuery=&DynamicListSortBy=xCreationDate&DynamicListSortOrder=Desc&DynamicListTitle=&PageNumber=1&Title=Antiepileptics%20&ResultCount=10

10.3 Monotherapy for newly diagnosed Focal Seizures

10.3.1 Introduction

Focal seizures are the most commonly encountered seizure type in adult and paediatric practice. Focal seizures are by definition those that originate in one area of the brain. The most recent proposal of the classification of the epilepsies by the ILAE has defined focal seizures as those that originate within networks limited to one hemisphere, and where for each seizure type ictal onset is consistent but preferential propagation patterns that can involve the contralateral hemisphere. (Berg et al 2010) [12]. The seizures are then described according to severity (e.g. with or without impairment of consciousness, or whether they proceed to a bilateral convulsive seizure) and possible site of origin.

When individuals first present, aims of treatment should be seizure freedom with one medication. The term monotherapy here refers to the use of one initial drug with no previous trial of such.

10.3.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence review. For this review we included adults and children with focal seizures. For studies in which both focal and primary generalized seizures were combined, a 20% threshold was used as a threshold for "contamination" for the outcome of seizure freedom and a 50% threshold for the outcomes of adverse events.

One high quality individual patient data network meta-analysis [38] was identified during stakeholder consultation. The GDG agreed that this was a high quality study that should be incorporated into the evidence review. The individual patient data for 6418 patients from 20 randomised controlled trials was incorporated into the evidence review for monotherapy in newly diagnosed focal seizures to complement the findings of the pair-wise meta-analyses and assist the GDG in terms of their decision-making and recommendation development.

10.3.3 Matrix of the evidence for adults

We searched for RCTs comparing the effectiveness of different monotherapy pharmacological interventions for epilepsy in a population with focal seizures. The interventions we included in our search were eslicarbazepine acetate, pregabalin, zonisamide, lacosamide, lamotrigine, gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbital, felbamate, clobazam, clonazepam, acetazolamide, primidone, sodium valproate, sulthiame and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter. It should be noted that some of the studies from the direct meta-analysis are the same as those in the IPD network meta-analysis.

Placebo											
Carbamazepine											
Carbamazepine-CR											
Clonazepam		1 [160];									
Gabapentin		2 [161,162,] 1 IPD NMA [38]									
Lamotrigine		6 [161,163,164,165,166,166,] 1 IPD NMA [38;]			1 [161,] 1 IPD NMA [38]						
Levetiracetam			1 [167]								
Oxcarbazepine		1 [161,] 1 IPD NMA [38]			1 [161,] 1 IPD NMA [38]	1 [161,] 1 IPD NMA [38]					
Phenytoin		4 [168,169,170,171,] 1 IPD NMA [38]			1 IPD NMA [38]	1 [172,] 1 IPD NMA [38]		1 [173,] 1 IPD NMA [38]			
Sodium valproate		2 [171,174], 1 IPD NMA [38]				1 IPD NMA [38]		1 [175,] 1 IPD NMA [38]	3 [171,176,177,] 1 IPD NMA [38]		
Topiramate		1 [161,] 1 IPD NMA [38]			1 [161,] 1 IPD NMA [38]	1 [161,] 1 IPD NMA [38]		1 [161,] 1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	
Vigabatrin		3 [178,179,180,]									

		1 IPD NMA [38]													
Tiagabine															
Phenobarbital		1 [170], 1 IPD NMA [38]			1 IPD NMA [38]			1 IPD NMA [38]	1 [170], 1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]				
Primidone		1 [170]							1 [170]					1 [170]	
	Pla	CBZ	CBZ- CR	CLZ	GBP	LTG	LEV	OXC	PHT	VPA	TPM	VGB	TGB	PHB	PMD

PLA - Placebo	CBZ - Carbamazepine	CBZ-CR – Controlled release Carbamazepine	CLZ - Clonazepam
GBP - Gabapentin	LTG - Lamotrigine	LEV - Levetiracetam	OXC - Oxcarbazepine
PHT - Phenytoin	VPA - Sodium valproate	TPM - Topiramate	VGB - Vigabatrin

IPD NMA: individual patient network meta-analysis

10.3.4 Monotherapy for adults with newly diagnosed focal seizures

10.3.4.1 Carbamazepine versus lamotrigine

Clinical evidence

For details on the clinical evidence please refer to Appendix N.

IPD meta-analysis

Carbamazepine and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health economic evidence

Two economic evaluations [161,181] of AEDs, including carbamazepine and lamotrigine, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, we developed an original economic model to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Carbamazepine monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to first seizure, although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Carbamazepine monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Time to treatment failure occurred significantly more rapidly in participants taking carbamazepine monotherapy compared to participants taking lamotrigine monotherapy. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between carbamazepine monotherapy and lamotrigine monotherapy for seizure freedom. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of participants who withdrew due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to 12-month remission. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to 12-month remission. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly more participants taking carbamazepine monotherapy withdrew due to adverse events compared to participants taking lamotrigine monotherapy. (MODERATE QUALITY)

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more rapidly in participants taking carbamazepine monotherapy compared to participants taking lamotrigine monotherapy. (VERY LOW QUALITY)

Significantly more participants taking carbamazepine monotherapy compared to participants taking lamotrigine monotherapy had incidence of:

- fatigue (LOW QUALITY)
- tiredness/drowsiness/fatigue/lethargy, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- allergic rash (MODERATE QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between lamotrigine monotherapy and carbamazepine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores (VERY LOW QUALITY)
- two year GQoL scores (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results

There was a significant improvement in phonemic fluency (COWAT) at 16 and 48 weeks for lamotrigine monotherapy relative to carbamazepine monotherapy.

There was a significant improvement in Stroop Color-Word Interference test at 48 weeks for lamotrigine monotherapy relative to carbamazepine monotherapy.

There was a significant improvement in the obsessive-compulsive scores at 48 weeks on the SCL-90 for carbamazepine monotherapy relative to lamotrigine monotherapy.

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between lamotrigine monotherapy and carbamazepine monotherapy.

No significant difference was found in other COWAT tests between lamotrigine monotherapy and carbamazepine monotherapy.

No significant difference was found in other SCL-90 tests between lamotrigine monotherapy and carbamazepine monotherapy.

Cost-effectiveness

Available economic evidence indicates that lamotrigine is cost effective when compared to carbamazepine.

- One trial-based economic analysis showed lamotrigine to be associated with increased costs but also better health outcomes (higher QALYs and fewer seizures) when compared with carbamazepine (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline found carbamazepine and lamotrigine to be very similar in terms of effectiveness, with carbamazepine associated with higher costs. This conclusion was sensitive to assumptions about the acquisition costs of lamotrigine and carbamazepine (directly applicable and minor limitations).
- A published cost-effectiveness analysis by Hawkins and colleagues found that carbamazepine dominated lamotrigine; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).

10.3.4.2 Lamotrigine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Lamotrigine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly on participants taking phenytoin monotherapy compared to participants taking lamotrigine monotherapy. (IPD meta-analysis indirect evidence)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to first seizure. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to first seizure. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly less participants taking lamotrigine monotherapy had an incidence of asthenia compared to participants in phenytoin monotherapy, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Significantly less participants taking lamotrigine monotherapy had an incidence of somnolence compared to participants in phenytoin monotherapy (VERY LOW QUALITY)

Significantly more participants taking phenytoin monotherapy had an incidence of ataxia compared to participants in lamotrigine monotherapy (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy for the incidence of the following adverse events:

- rash (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)

Quality of life outcomes– statistically significant results

Significantly more participants on lamotrigine monotherapy had improvement in the overall score of SEALS compared to phenytoin monotherapy in 24 weeks treatment (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to phenytoin monotherapy was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to exit/withdrawal of allocated treatment
- cognitive outcomes

10.3.4.3 Levetiracetam versus controlled-release carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As this left a gap in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. This was based on (see section 10.3.5) the results of the systematic review of clinical evidence. The complete results of the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in levetiracetam monotherapy withdrew due to lack of efficacy compared to controlled-release carbamazepine monotherapy (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between levetiracetam monotherapy and controlled-release carbamazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant

No significant difference between levetiracetam monotherapy and controlled-release carbamazepine monotherapy for the withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between levetiracetam monotherapy and controlled-release carbamazepine monotherapy for the incidence of:

- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing levetiracetam to controlled-release carbamazepine was identified. However, available economic evidence indicates that levetiracetam, at its current 2011 cost, is not cost effective when compared to carbamazepine (directly applicable and minor limitations).

- A cost-effectiveness analysis undertaken for the guideline found that at June 2011 costs, levetiracetam is not cost effective when compared to carbamazepine. This conclusion was robust to various sensitivity analyses including those that were favourable towards levetiracetam.
  - If carbamazepine was assumed to be more tolerable than levetiracetam, it dominated levetiracetam; that is, treatment with carbamazepine was associated with lower costs and better health outcomes (higher QALYs) than treatment with levetiracetam.
  - If carbamazepine was assumed to be less tolerable than levetiracetam, then levetiracetam was more effective, but had an incremental cost-effectiveness ratio of £332,152 which exceeds the NICE willingness to pay threshold of £20,000 per QALY gained.
- Only if levetiracetam can be acquired for 70 percent less than its June 2011 unit cost is it potentially cost effective when compared with carbamazepine. Note that when all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.3.4.4 Carbamazepine versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [161] of AEDs, including carbamazepine and gabapentin, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy- statistically significant results

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly more rapidly in participants taking gabapentin monotherapy compared to participants taking carbamazepine monotherapy. (MODERATE QUALITY)

Carbamazepine monotherapy is significantly more effective than gabapentin monotherapy in prolonging time to first seizure. (MODERATE QUALITY)

Carbamazepine monotherapy is significantly more effective than gabapentin monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Time to 12-month remission occurred significantly more rapidly on carbamazepine monotherapy compared to gabapentin monotherapy. (MODERATE QUALITY)

Time to 12-month remission occurred significantly more rapidly on carbamazepine monotherapy compared to gabapentin monotherapy. (IPD meta-analysis)

Efficacy- statistically non-significant results

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for time to treatment failure. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly fewer patients withdrew due to adverse events with gabapentin monotherapy compared to carbamazepine monotherapy. (MODERATE QUALITY)

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly less rapidly on participants taking gabapentin monotherapy compared to participants taking carbamazepine monotherapy. (MODERATE QUALITY)

Significantly more patients on carbamazepine monotherapy had incidence of allergic rash compared to gabapentin monotherapy. (MODERATE QUALITY)

Adverse events – statistically non- significant results

No significant difference between carbamazepine monotherapy and gabapentin monotherapy for incidence of tiredness/drowsiness/fatigue/lethargy (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between gabapentin monotherapy and carbamazepine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores (VERY LOW QUALITY)
- two year GQoL scores (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between gabapentin monotherapy and carbamazepine monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that gabapentin is not cost effective when compared to carbamazepine.

- One trial-based economic evaluation found that carbamazepine dominated gabapentin; that is, treatment with carbamazepine was associated with lower costs and better health outcomes (higher QALYs and fewer seizures) than treatment with gabapentin (partially applicable and had potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline also showed that carbamazepine dominated gabapentin. This conclusion was robust to various sensitivity analyses. Note that when all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources (directly applicable and had minor limitations).

10.3.4.5 Vigabatrin versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but vigabatrin was not. Vigabatrin was excluded owing to its potential for long term adverse effects.

Evidence statements

Efficacy- statistically significant results

Significantly more patients were seizure free with carbamazepine monotherapy than vigabatrin monotherapy, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Significantly fewer patients withdrew due to lack of efficacy with carbamazepine monotherapy than vigabatrin monotherapy. (VERY LOW QUALITY)

Carbamazepine monotherapy is significantly more effective than vigabatrin monotherapy in prolonging time to first seizure. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between vigabatrin monotherapy and carbamazepine monotherapy for time to exit/withdrawal of allocated treatment. (VERY LOW QUALITY)

Adverse events - statistically significant results

Significantly more participants on carbamazepine monotherapy compared to vigabatrin monotherapy withdrew due to adverse events. (VERY LOW QUALITY)

Significantly more participants on carbamazepine monotherapy compared to vigabatrin monotherapy experienced drowsiness, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

There was no significant difference between vigabatrin monotherapy and carbamazepine monotherapy for the incidence of the following adverse events:

- fatigue (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- appendages (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- generalised rash (VERY LOW QUALITY)
- visual disturbances (VERY LOW QUALITY)
- myoclonic jerks (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.3.4.6 Clonazepam versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but clonazepam was not included due to the lack of efficacy data reported in the trial.

Evidence statements

Adverse events – statistically non-significant results

No significant difference between clonazepam monotherapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing clonazepam and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.3.4.7 Oxcarbazepine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Oxcarbazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly in participants taking phenytoin monotherapy compared to participants taking oxcarbamazepine monotherapy. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse effects – statistically significant results

Significantly fewer participants in oxcarbazepine monotherapy withdrew due to adverse events compared to participants in phenytoin monotherapy. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing oxcarbazepine and phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.3.4.8 Oxcarbazepine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Oxcarbazepine and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [181] of AEDs, including oxcarbazepine and sodium valproate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse events – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that oxcarbazepine is not cost effective when compared to sodium valproate.

- A published cost-effectiveness analysis by Hawkins and colleagues found that oxcarbazepine was more effective than sodium valproate, but with an unacceptably high incremental cost-effectiveness ratio of £156,545 per QALY; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline also showed that oxcarbazpeine was more effective and more costly than sodium valproate, but with a much lower incremental cost-effectiveness ratio of £37,551 per QALY. This value still exceeds the NICE willingness to pay threshold of £20,000 per QALY gained. When all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources. This conclusion was consistent across various sensitivity analyses.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.3.4.9 Phenobarbital versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and phenobarbital were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to the lack of efficacy data reported in the trial.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly in participants taking phenobarbital monotherapy compared to participants taking carbamazepine monotherapy. (IPD meta-analysis)

Phenobarbital monotherapy is significantly more effective than carbamazepine monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the time to 12-month remission. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenobarbital and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- incidence of adverse events
- quality of life outcomes
- cognitive outcomes.

10.3.4.10 Primidone versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but primidone was not due to the lack of efficacy data reported in the trial.

Evidence statements

Adverse effects – statistically significant results

Significantly more participants in the primidone monotherapy group withdrew due to adverse events compared to participants in the carbamazepine monotherapy group. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing primidone and carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- quality of life outcomes
- cognitive outcomes.

10.3.4.11 Phenytoin versus phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and phenobarbital were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Neither phenytoin nor phenobarbital was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. Phenytoin was excluded owing to its narrow therapeutic window and phenobarbital was excluded due to the lack of efficacy data reported in the evidence.

Evidence statements

Efficacy – statistically significant results

Phenobarbital monotherapy is significantly more effective than phenytoin monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between phenytoin monotherapy and phenobarbital monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and phenobarbital monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between phenytoin monotherapy and phenobarbital monotherapy for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenytoin and phenobarbital was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- incidence of adverse events
- quality of life outcomes
- cognitive outcomes.

10.3.4.12 Phenytoin versus primidone

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Neither phenytoin nor primidone was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. Phenytoin was excluded owing to its narrow therapeutic window and primidone was excluded due to the lack of efficacy data reported in the evidence.

Evidence statements

Adverse effects – statistically significant results

Significantly more participants in the primidone monotherapy group withdrew due to adverse events compared to participants in the phenytoin monotherapy group. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing phenytoin and primidone was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- quality of life outcomes
- cognitive outcomes.

10.3.4.13 Phenobarbital versus primidone

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Neither phenobarbital nor primidone were included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures due to the lack of efficacy data reported in the evidence.

Evidence statements

Adverse effects – statistically significant results

Significantly more participants in the primidone monotherapy group withdrew due to adverse events compared to participants in the phenobarbital monotherapy group. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing phenobarbital and primidone was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- quality of life outcomes
- cognitive outcomes

10.3.4.14 Carbamazepine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and phenytoin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Carbamazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants (VERY LOW QUALITY).

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing carbamazepine and phenytoin was identified.

Cognitive outcomes – statistically non-significant results

No significant difference between carbamazepine monotherapy and phenytoin monotherapy for any of the cognitive test outcomes:

- digit symbol (VERY LOW QUALITY)
- digit span forward (VERY LOW QUALITY)
- digit span backward (VERY LOW QUALITY)
- Consistent Long Term Retrieval Score (VERY LOW QUALITY)
- Finger Tap (VERY LOW QUALITY)
- Grooved Pegboard (VERY LOW QUALITY)
- Choice Reaction Time (VERY LOW QUALITY)
- P3 latency (VERY LOW QUALITY)
- P3 amplitude (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- quality of life outcomes.

10.3.4.15 Carbamazepine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [181] of AEDs, including carbamazepine and sodium valproate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to 12-month remission occurred significantly more rapidly on carbamazepine monotherapy compared to sodium valproate monotherapy. (IPD meta-analysis)

Carbamazepine monotherapy is significantly more effective than sodium valproate monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and sodium valproate monotherapy for time to treatment failure. (IPD meta-analysis)

Cognitive outcomes – statistically non-significant results

No significant differences between carbamazepine and sodium valproate for any of the following cognitive outcomes: motor, speed and integration, memory, concentration and mental flexibility after 6 months of treatment.

Cost-effectiveness

Available economic evidence indicates that carbamazepine is cost effective when compared to sodium valproate.

- The cost-effectiveness analysis undertaken for the guideline showed that treatment with carbamazepine was associated with increased costs and better health outcomes (higher QALYs) than treatment with sodium valproate, with an expected incremental cost-effectiveness ratio of £7,512. This conclusion was consistent across various sensitivity analyses. However, when all relevant comparators were evaluated together, lamotrigine was likely to represent the most cost-effective use of NHS resources (directly applicable and minor limitations).
- The study by Hawkins and colleagues found sodium valproate to be more cost-effective than carbamazepine; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- incidence of adverse events
- quality of life outcomes.

10.3.4.16 Sodium valproate versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Sodium valproate was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not. Phenytoin was excluded owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the time to treatment failure. (IPD meta-analysis)

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between sodium valproate monotherapy and phenytoin monotherapy for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate and phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.3.4.17 Carbamazepine versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and topiramate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including carbamazepine and topiramate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly more rapidly on topiramate monotherapy compared to carbamazepine monotherapy, although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Efficacy – statistically non significant results

No significant difference between carbamazepine monotherapy and topiramate monotherapy for time to treatment failure (IPD meta-analysis).

No significant difference between carbamazepine monotherapy and topiramate monotherapy for time to first seizure. (VERY LOW QUALTY)

No significant difference between carbamazepine monotherapy and topiramate monotherapy for time to first seizure. (IPD meta-analysis)

No significant difference between carbamazepine monotherapy and topiramate monotherapy for time to 12-month remission. (LOW QUALITY)

No significant difference between carbamazepine monotherapy and topiramate monotherapy for time to 12-month remission. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly more participants taking carbamazepine monotherapy compared to topiramate monotherapy had incidence of allergic rash. (MODERATE QUALITY)

Adverse events – statistically non significant results

No significant difference between carbamazepine monotherapy and topiramate monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and topiramate monotherapy for incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically significant results

Topiramate monotherapy had a significantly reduced score compared to carbamazepine monotherapy in the two year anxiety scores, although there is uncertainty over the magnitude of its clinical effect. (MODERATE QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between carbamazepine monotherapy and topiramate monotherapy in:

- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores. (VERY LOW QUALITY)
- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between topiramate monotherapy and carbamazepine monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that topiramate is unlikely to be considered cost effective when compared with carbamazepine, however there is uncertainty in this conclusion.

- One economic evaluation conducted alongside a randomised controlled trial showed that treatment with topiramate was associated with increased costs and better health outcomes (higher QALYs) compared to carbamazepine. However the same analysis showed that patients receiving topiramate experienced more seizures than patients receiving carbamazepine. When all comparators from the trial were evaluated together, topiramate was dominated by oxcarbazepine; that is, oxcarbazepine produced greater QALY gains (and fewer seizures) at a lower cost (partially applicable and potentially serious limitations).
- One published cost-effectiveness analysis showed topiramate to be more costly and more effective than carbamazepine, but with an unacceptably high incremental cost-effectiveness ratio (£89,736 per QALY) (partially applicable and potentially serious limitations); however, this analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- Results of the cost-effectiveness analysis undertaken for the guideline found that topiramate was not cost effective compared to carbamazepine. Carbamazepine dominated topiramate; that is, treatment with carbamazepine was associated with lower costs and better health outcomes (higher QALYs) than treatment with topiramate. This conclusion was robust to various sensitivity analyses. Note that when all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources (directly applicable and minor limitations).

10.3.4.18 Topiramate versus sodium valproate

Clinical evidence

No clinical evidence was identified.

IPD meta-analysis

Topiramate and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [181] of AEDs, including topiramate and sodium valproate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Efficacy – statistically non significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between topiramate monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

Cost-effectiveness

Available economic evidence indicates that topiramate is not cost effective when compared to sodium valproate.

- A cost-effectiveness analysis undertaken for the guideline found that sodium valproate dominated topiramate; that is, treatment with sodium valproate was associated with lower costs and better health outcomes (higher QALYs) than treatment with topiramate. However, when all relevant comparators were evaluated together, lamotrigine was likely to represent the most cost-effective use of NHS resources. This conclusion was consistent across various sensitivity analyses (directly applicable and minor limitations).
- The cost-effectiveness analysis by Hawkins and colleagues found topiramate to be more effective, although not cost effective, compared to sodium valproate, but their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- quality of life outcomes
- cognitive outcomes.

10.3.4.19 Carbamazepine versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Carbamazepine and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including carbamazepine and oxcarbazepine, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to treatment failure. (IPD meta-analysis)

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the proportion of participants who withdrew due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to first seizure. (VERY LOW QUALITY).

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to first seizure. (IPD meta-analysis)

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to 12-month remission. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for the time to 12-month remission. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between carbamazepine monotherapy and oxcarbazepine monotherapy for incidence of:

- tiredness/drowsiness/fatigue/lethargy (VERY LOW QUALITY)
- allergic rash (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between oxcarbazepine monotherapy and topiramate monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores. (VERY LOW QUALITY)
- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between oxcarbazepine monotherapy and carbamazepine monotherapy.

Cost-effectiveness

Available economic evidence indicates that oxcarbazepine may be cost effective when compared to carbamazepine, but the conclusion is dependent on the threshold willingness to pay.

- One trial-based economic evaluation showed oxcarbazepine to be cost-effective compared to carbamazepine, with an incremental cost-effectiveness ratio of £6,200 per QALY (partially applicable and potentially serious limitations).
- One published cost-effectiveness analysis found oxcarbazepine to be more costly and more effective than carbamazepine but with an unacceptably high incremental cost-effectiveness ratio of £81,130 per QALY; however, this analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis developed for the guideline also found oxcarbazepine to be more costly and more effective than carbamazepine, with an unacceptably high incremental cost-effectiveness ratio of £127,224 per QALY. This conclusion was consistent across various sensitivity analyses. Note that when all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources.

10.3.4.20 Gabapentin versus lamotrigine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [161] of AEDs, including gabapentin and lamotrigine, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less rapidly in participants taking lamotrigine monotherapy compared to participants taking gabapentin monotherapy. (MODERATE QUALITY)

Time to treatment failure occurred significantly less rapidly in participants taking lamotrigine monotherapy compared to participants taking gabapentin monotherapy. (IPD meta-analysis)

Time to 12-month remission occurred significantly more rapidly on lamotrigine monotherapy compared to gabapentin monotherapy although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the proportion of participants who withdrew due to lack of efficacy. (LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the proportion of seizure free participants. (LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for time to first seizure. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for time to first seizure. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse effects – statistically significant results

Significantly less participants taking lamotrigine monotherapy compared to participants taking gabapentin monotherapy had an increase in body weight, although there is uncertainty over the magnitude of its clinical effect. (MODERATE QUALITY)

Significantly less participants taking gabapentin monotherapy compared to participants taking lamotrigine monotherapy had skin rash, although there is uncertainty over the magnitude of its clinical effect. (MODERATE QUALITY)

Adverse effects – statistically non-significant results

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the proportion of participants who withdrew due to adverse events. (LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and lamotrigine monotherapy for the incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically significant results

Lamotrigine monotherapy had a significantly reduced score compared to gabapentin monotherapy in the two year depression ordinal scores. (MODERATE QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between gabapentin monotherapy and lamotrigine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores (VERY LOW QUALITY)
- two year GQoL scores (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between gabapentin monotherapy and lamotrigine monotherapy.

Cost-effectiveness

Available economic evidence indicates that gabapentin is not cost effective when compared with lamotrigine.

- One economic evaluation conducted alongside a randomised controlled trial showed lamotrigine dominated gabapentin; that is, treatment with lamotrigine was associated with lower costs and better health outcomes (higher QALYs and fewer seizures) than treatment with gabapentin (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis developed for the guideline also showed that lamotrigine dominated gabapentin. This conclusion was consistent across various sensitivity analyses (directly applicable and minor limitations).

10.3.4.21 Gabapentin versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and topiramate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [161] of AEDs, including gabapentin and topiramate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less rapidly in participants taking topiramate monotherapy compared to participants taking gabapentin monotherapy. (MODERATE QUALITY)

Topiramate monotherapy is significantly more effective than gabapentin monotherapy in prolonging the time to first seizure. (MODERATE QUALITY).

Topiramate monotherapy is significantly more effective than gabapentin monotherapy in prolonging the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and topiramate monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and topiramate monotherapy for the time to 12-month remission. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and topiramate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and topiramate monotherapy for time to treatment failure. (IPD meta-analysis)

Adverse effects – statistically significant results

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more rapidly on participants taking topiramate monotherapy compared to participants taking gabapentin monotherapy. (MODERATE QUALITY)

Adverse effects – statistically non-significant results

No significant difference between gabapentin monotherapy and topiramate monotherapy for the incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically significant results

Topiramate monotherapy had significantly reduced scores compared to gabapentin monotherapy in the anxiety scores, although there is uncertainty in the magnitude of clinical effect. (MODERATE QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between gabapentin monotherapy and topiramate monotherapy in:

- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores (VERY LOW QUALITY)
- two year GQoL scores (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between gabapentin monotherapy and topiramate monotherapy.

Cost-effectiveness

Available economic evidence indicates that topramate may not be cost effective when compared to gabapentin, but there is uncertainty in this conclusion.

- One economic evaluation conducted alongside a randomised controlled trial showed that topiramate dominated gabapentin; that is, treatment with gabapentin was to be more costly and less effective (fewer QALYs and more seizures) than treatment with topiramate (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that topiramate was not cost effective compared to gabapentin. Although topiramate was found to be more effective, it had an incremental cost-effectiveness ratio of £41,868 per QALY, which exceeds the NICE willingness to pay threshold of £20,000 per QALY gained. However, in the NCGC analysis, both topiramate and gabapentin were more costly and less effective than carbamazepine, lamotrigine and sodium valproate (directly applicable and minor limitations).

10.3.4.22 Lamotrigine versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including lamotrigine and topiramate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly in participants taking topiramate monotherapy compared to participants taking lamotrigine monotherapy. (IPD meta-analysis)

Topiramate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and topiramate monotherapy for time to first seizure. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and topiramate monotherapy for time to 12-month remission. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and topiramate monotherapy for time to 12-month remission. (IPD meta-analysis)

Adverse effects – statistically significant results

Time to exit/withdrawal of allocated treatment due to adverse events occurred significantly more rapidly on participants taking topiramate monotherapy compared to participants taking lamotrigine monotherapy. (MODERATE QUALITY)

Adverse effects – statistically non significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy for the incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between lamotrigine monotherapy and topiramate monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores. (VERY LOW QUALITY)

- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between lamotrigine monotherapy and topiramate monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that lamotrigine is cost-effective when compared with topiramate.

- One trial-based economic evaluation showed lamotrigine to be more costly and more effective (higher QALYs and fewer seizures) than topiramate with an incremental cost-effectiveness ratio of £6,727 per QALY (partially applicable and potentially serious limitations). However, both topiramate and lamotrigine were more costly and less effective than oxcarbazepine in this analysis. Since the analysis was undertaken, lamotrigine and topiramate have come off patent and their unit costs have come down considerably (partially applicable and potentially serious limitations).
- One published cost-effectiveness analysis found that lamotrigine dominated topiramate; that is, treatment with lamotrigine was associated with lower costs and better outcomes (higher QALYs) than treatment with topiramate; however, this analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline also found that lamotrigine dominated topiramate. This conclusion was consistent across various sensitivity analyses (directly applicable and minor limitations).

10.3.4.23 Gabapentin versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [161] of AEDs, including oxcarbazepine and gabapentin, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of this study and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Time to exit/withdrawal of allocated treatment due to lack of efficacy occurred significantly less rapidly in participants taking oxcarbazepine monotherapy compared to participants taking gabapentin monotherapy. (MODERATE QUALITY)

Time to treatment failure occurred significantly less rapidly in participants taking oxcarbazepine monotherapy compared to participants taking gabapentin monotherapy. (IPD meta-analysis)

Oxcarbazepine monotherapy is significantly more effective than gabapentin monotherapy in prolonging time to first seizure, although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Oxcarbazepine monotherapy is significantly more effective than gabapentin monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Time to 12-month remission occurred significantly more rapidly on oxcarbazepine monotherapy than gabapentin monotherapy. (MODERATE QUALITY)

Time to 12-month remission occurred significantly more rapidly on oxcarbazepine monotherapy than gabapentin monotherapy. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for the incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between gabapentin monotherapy and oxcarbazepine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores. (VERY LOW QUALITY)
- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between gabapentin monotherapy and oxcarbazepine topiramate monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that oxcarbazepine is cost effective when compared to gabapentin.

- One trial-based economic evaluation found that oxcarbazepine dominated gabapentin; that is, treatment with oxcarbazepine was associated with lower costs and better health outcomes (higher QALYs and fewer seizures) than treatment with gabapentin (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed oxcarbazepine to be more costly and more effective than gabapentin, with an incremental cost-effectiveness ratio of £13,887 per QALY gained. This conclusion was consistent across various sensitivity analyses. However, when all relevant comparators were evaluated together in the NCGC analysis, lamotrigine was likely to represent the most cost-effective use of NHS resources(directly applicable and minor limitations).

10.3.4.24 Lamotrigine versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Oxcarbazepine and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including lamotrigine and oxcarbazepine, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Oxcarbazepine monotherapy is significantly more effective than lamotrigine monotherapy in prolonging the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the time to treatment failure. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to first seizure. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to 12-month remission. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to 12-month remission. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for the incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)

- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores (VERY LOW QUALITY)
- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between lamotrigine monotherapy and oxcarbazepine monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that oxcarbazepine may be cost effective when compared to lamotrigine, but evidence is conflicting; hence, there is considerable uncertainty in this conclusion.

- One trial-based economic evaluation found that oxcarbazepine dominated lamotrigine; that is, treatment with oxcarbazepine was associated with lower costs and better health outcomes (higher QALYs and fewer seizures) than treatment with lamotrigine (partially applicable and potentially serious limitations).
- One published cost-effectiveness analysis undertaken by Hawkins and colleagues found oxcarbazepine be more costly and more effective than lamotrigine, with an incremental cost-effectiveness ratio of £4,879 per QALY gained. However, this analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- The cost-effectiveness analysis developed for the guideline found that oxcarbazepine was not cost-effective compared to lamotrigine. Although oxcarbazepine was found to be more effective, it had an incremental cost-effectiveness ratio of £180,137 per QALY, which far exceeds the NICE willingness to pay threshold of £20,000 per QALY gained. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

10.3.4.25 Topiramate versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including topiramate and oxcarbazepine, used as monotherapy in the treatment of adults with newly diagnosed focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the time to treatment failure. (IPD meta-analysis)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to first seizure. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to first seizure. (IPD meta-analysis)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to 12-month remission. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to 12-month remission. (IPD meta-analysis)

Adverse effects – statistically non-significant results

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for the time to exit/withdrawal of allocated treatment due to adverse events. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for incidence of tiredness/drowsiness/fatigue/lethargy. (VERY LOW QUALITY)

Quality of Life outcomes – statistically non-significant results

There is no significant difference between topiramate monotherapy and oxcarbazepine monotherapy in:

- two year anxiety scores (VERY LOW QUALITY)
- two year depression scores (VERY LOW QUALITY)
- two year AEP scores (VERY LOW QUALITY)
- two year EQ-5D scores. (VERY LOW QUALITY)
- two year GQoL scores. (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

No significant difference was found on the mean scores of neurotoxicity scale scores between topiramate monotherapy and oxcarbazepine monotherapy.

Cost-effectiveness

Available economic evidence indicates that topiramate is not cost effective compared to oxcarbazepine.

- Results of a trial-based economic evaluation found oxcarbazepine dominated topiramate; that is, treatment with oxcarbazepine was associated with lower costs and better health outcomes (higher QALYs and fewer seizures) than treatment with topiramate (partially applicable and potentially serious limitations).
- One published cost-effectiveness analysis undertaken by Hawkins and colleagues showed topiramate was to be more costly and more effective than oxcarbazepine, but with an unacceptably high incremental cost-effectiveness ratio of £102,933 per QALY gained. However, this analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).

- The cost-effectiveness analysis developed for the guideline found that oxcarbazepine was cost-effective compared to topiramate. Under base case costing assumptions, oxcarbazepine dominated topiramate. And under alternative costing assumptions, which were favourable to topiramate, oxcarbazepine was more costly and more effective, but with an incremental cost-effectiveness ratio under the NICE willingness to pay threshold of £20,000 per QALY gained. However, when all relevant comparators were evaluated together, lamotrigine was likely to represent the most cost-effective use of NHS resources (directly applicable and minor limitations).

10.3.4.26 Lamotrigine versus phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Lamotrigine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to the lack of efficacy data reported in the trial.

Evidence statements

Efficacy – statistically significant results

Lamotrigine monotherapy is significantly more effective than phenobarbital monotherapy in prolonging the time to exit/withdrawal. (IPD meta-analysis)

Phenobarbital monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenobarbital monotherapy for the time to 12 month remission. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing phenobarbital and lamotrigine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.27 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Sodium valproate and lamotrigine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [181] of AEDs, including lamotrigine and sodium valproate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically significant results

Lamotrigine monotherapy is significantly more effective than sodium valproate monotherapy in prolonging the time to exit/withdrawal. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

Available economic evidence indicated that lamotrigine was cost effective when compared to sodium valproate

- A cost-effectiveness analysis undertaken for the guideline found that lamotrigine dominated sodium valproate; that is, treatment with lamotrigine was associated with lower costs and better health outcomes (higher QALYs) than treatment with sodium valproate. This conclusion was consistent across various sensitivity analyses.
- A published cost-effectiveness analysis by Hawkins and colleagues found that sodium valproate dominated lamotrigine, but their analysis was based on a now out-of-date systematic review and 2002-03 costs.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes

- quality of life outcomes

10.3.4.28 Oxcarbazepine versus phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Oxcarbazepine and phenobarbital were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Oxcarbazepine was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to the lack of efficacy data reported in the trial.

Evidence statements

Efficacy – statistically significant results

Oxcarbazepine monotherapy is significantly more effective than phenobarbital monotherapy in prolonging the time to exit/withdrawal. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and phenobarbital monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and phenobarbital monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing oxcarbazepine and phenobarbital was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.29 Phenobarbital versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Sodium valproate was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to the lack of efficacy data reported in the trial.

Evidence statements

Efficacy – statistically significant results

Sodium valproate monotherapy is significantly more effective than phenobarbital monotherapy in prolonging the time to exit/withdrawal. (IPD meta-analysis)

Sodium valproate monotherapy is significantly more effective than phenobarbital monotherapy for reducing the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between sodium valproate monotherapy and phenobarbital monotherapy for the time to 12 month remission. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing sodium valproate and phenobarbital was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.30 Gabapentin versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

One economic evaluation [181] of AEDs, including gabapentin and sodium valproate, used as monotherapy in the treatment of adults with newly diagnosed focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed focal seizures. The complete results of these studies and the NCGC adult monotherapy model are presented in section 10.3.6.

Evidence statements

Efficacy – statistically non-significant results

No significant didfference between gabapentin monotherapy and sodium valproate monotherapy for time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and sodium valproate monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and sodium valproate monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

Available economic evidence indicates that gabapentin is not cost effective when compared to sodium valproate.

- A cost-effectiveness analysis undertaken for the guideline showed that sodium valproate dominated gabapentin; that is, treatment with sodium valproate was associated with lower costs and better health outcomes (higher QALYs) than treatment with gabapentin. However, when all relevant comparators were evaluated together, lamotrigine was likely to represent the most cost-effective use of NHS resources. This conclusion was consistent across various sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.31 Phenobarbital versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and topiramate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Topiramate was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to a lack of efficacy data.

Evidence statements

Efficacy – statistically significant results

Topiramate monotherapy is significantly more effective than phenobarbital monotherapy in prolonging the time to exit/withdrawal. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and topiramate monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and topiramate monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing topiramate and phenobarbital was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.32 Phenytoin versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and topiramate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Topiramate was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not due to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant didfference between phenytoin monotherapy and topiramate monotherapy for time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and topiramate monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and topiramate monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing topiramate and phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.33 Phenobarbital versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Gabapentin was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenobarbital was not due to a lack of efficacy data.

Evidence statements

Efficacy – statistically significant results

Phenobarbital monotherapy is significantly more effective than gabapentin monotherapy in prolonging the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and gabapentin monotherapy for time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and gabapentin monotherapy for the time to 12 month remission. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing gabapentin and phenobarbital was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.4.34 Phenytoin versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed focal seizures. The results of this analysis are presented in section 10.3.5.

Health Economic Evidence

No studies were identified in the economic literature search. Gabapentin was included in the original economic model developed to compare AEDs used as monotherapy in adults with newly diagnosed focal seizures, but phenytoin was not due to its narrow therapeutic window.

Evidence statements

Efficacy – statistically significant results

Phenytoin monotherapy is significantly more effective than gabapentin monotherapy in prolonging the time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between phenytoin monotherapy and gabapentin monotherapy for time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and gabapentin monotherapy for the time to 12 month remission. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing gabapentin and phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes

10.3.5 Individual patient data network meta-analysis as monotherapy for focal epilepsy

During the literature review we identified a network meta-analysis of Individual Patient Data (IPD). It included IPD evidence from randomized controlled trials of eight different AEDs (carbamazepine, sodium valproate, phenytoin, phenobarbital, oxcarbazepine, lamotrigine, gabapentin and topiramate) in monotherapy of focal seizures (Tudur Smith et al, 2007)[38]. It should be recognised that this was a network meta-analyses which combines direct and indirect analyses.

The data on direct comparisons came from eight Cochrane studies including direct analyses of carbamazepine versus sodium valproate, phenytoin versus sodium valproate, carbamazepine versus phenytoin, phenytoin versus phenobarbitone, carbamazepine versus phenobarbitone, sodium valproate versus phenobarbitone, oxcarbazepine versus phenytoin and lamotrigine versus carbamazepine. Direct evidence was not available for some pair-wise comparisons such as oxcarbazepine versus lamotrigine or phenobarbital, as there was no randomised controlled trials available at the time of writing the Cochrane reviews. Also trials comparing drugs such as oxcarbamazepine versus phenobarbitone are unlikely to be conducted in the future because of changing 'fashions' for treatment (Tudur Smith et al, 2007)[38].

The outcomes included were time to treatment failure due to inadequate seizure control, intolerable adverse effects or a combination of both; time to 12 month remission from seizures (days from randomisation and end of a period of 12 months without seizures); and time to first seizure after randomisation. It included data from 4265 focal participants for time to treatment failure, 3526 focal participants for time to 12 month remission and 2959 focal participants for time to first seizure. The following tables show the results for the various outcomes, comparing each AED with the current standard AED, carbamazepine. The significant results are highlighted in bold.

Time to treatment failure

Intervention	Comparator	Hazard ratio (95% CI)
Lamotrigine	Carbamazepine	**0.70 (0.58 to 0.83)**
Oxcarbazepine	Carbamazepine	0.88 (0.69 to 1.12)
Sodium valproate	Carbamazepine	1.00 (0.82 to 1.24)
Topiramate	Carbamazepine	1.13 (0.93 to 1.37)
Gabapentin	Carbamazepine	1.16 (0.96 to 1.41)
Phenytoin	Carbamazepine	1.24 (0.98 to 1.57)
Phenobarbital	Carbamazepine	**1.60 (1.22 to 2.10)**

(a) HR<1 CBZ worse; HR >1 CBZ better

When compared with all the AEDs in the IPD analysis lamotrigine was found to be significantly better compared to other AEDs except from oxcarbazepine for time to treatment failure.

Time to 12 month remission

Intervention	Comparator	Hazard ratio
Carbamazepine	Oxcarbazepine	1.00 (0.82 to 1.22)
Carbamazepine	Phenobarbital	1.01 (0.77 to 1.31)
Carbamazepine	Phenytoin	1.15 (0.94 to 1.41)
Carbamazepine	Lamotrigine	1.15 (0.96 to 1.37)
Carbamazepine	Topiramate	1.19 (0.99 to 1.43)
Carbamazepine	Sodium valproate	**1.20 (1.01 to 1.42)**
Carbamazepine	Gabapentin	**1.38 (1.15 to 1.67)**

(a) HR<1 CBZ worse; HR >1 CBZ better

Carbamazepine was found to be significantly better than sodium valproate and gabapentin for time to 12 month remission.

Time to first seizure

Intervention	Comparator	Hazard ratio
Phenobarbital	Carbamazepine	**0.77 (0.61 to 0.96)**
Oxcarbazepine	Carbamazepine	0.99 (0.83 to 1.19)
Topiramate	Carbamazepine	1.00 (0.85 to 1.18)
Phenytoin	Carbamazepine	1.04 (0.88 to 1.24)
Sodium valproate	Carbamazepine	**1.23 (1.06 to 1.41)**
Lamotrigine	Carbamazepine	**1.29 (1.13 to 1.48)**
Gabapentin	Carbamazepine	**1.35 (1.15 to 1.59)**

(a) HR<1 CBZ worse; HR >1 CBZ better

Carbamazepine was found to be significantly better than sodium valproate, lamotrigine and gabapentin for time to first seizure. Phenobarbital was significantly better than carbamazepine.

Further data showing each AED comparison for the three outcomes of the IPD are presented in appendix N.

10.3.6 Health economic evidence of AEDs used as monotherapy for adults with newly diagnosed focal epilepsy

Two studies [161,181] assessing the cost-effectiveness of AEDs used as monotherapy were included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability. Following the review of the clinical and cost-effectiveness literature, it was considered that most AEDs were broadly similar in their efficacy, but evidence of their cost-effectiveness was limited and, at times, conflicting. Given these limitations in the evidence base, an original economic model was developed to compare AEDs used as first-line monotherapy in adults with newly diagnosed focal epilepsy. This was based on evidence from the Tudur Smith network meta-analysis (see section 10.3.5) and clinical review detailed above. See appendix P for full details and results of modelling.

Economic study characteristics

Table 1: Monotherapy for adults with newly diagnosed focal epilepsy - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCGC Model - adult monotherapy (see Appendix P for details)	Minor limitations	Directly applicable	Decision analytic model; comparators included carbamazepine, carbamazepine controlled release, oxcarbazepine, sodium valproate, lamotrigine, topiramate and levetiracetam; time horizon 15 years; clinical data based on Tudur Smith network meta-analysis and Brodie 2007 (see appendix P for details)
Marson (2007) – after	Potentially serious	Partially applicable (c)	Economic evaluation alongside

Study	Limitations	Applicability	Other Comments
June 2001[161]	limitations (a, b)		randomised controlled trial; cost per QALY analysis; comparators included carbamazepine, lamotrigine, gabapentin, topiramate and oxcarbazepine; 2-year time horizon; includes data collected after June 2001 when oxcarbazepine was introduced
Marson (2007) – after June 2001[161]	Potentially serious limitations (a, b)	Partially applicable (d)	Economic evaluation alongside randomised controlled trial; cost per seizure avoided analysis; comparators included carbamazepine, lamotrigine, gabapentin, topiramate and oxcarbazepine; 2-year time horizon; includes data collected after June 2001 when oxcarbazepine was introduced
Hawkins (2005)[181]	Potentially serious limitations (a, c, e)	Partially applicable (f)	Decision analytic model; comparators included carbamazepine, oxcarbazepine, sodium valproate, lamotrigine and topiramate; time horizon 15 years; clinical data based on network meta-analysis that included several studies with mixed focal and generalised epilepsy populations

(a) Unit costs of interventions are from 2002/03 (in Hawkins) and 2005 (in Marson) and since publication, lamotrigine and topiramate have come off patent and the non-proprietary price is dramatically lower
(b) Responders to EQ-5D questionnaires at 2 year follow-up were 'healthier' than non-responders
(c) The study did not include all comparators of interest to the GDG, namely levetiracetam.
(d) Analysis based on seizures avoided, not QALYs
(e) Effectiveness data was derived from a network meta-analysis that included one study that was not included in the NCGC clinical review (Beunanen 1996).
(f) Costs and effects discounted at 6% and 1.5% per annum, respectively.

Economic study results

NCGC Model – adult monotherapy (directly applicable, minor limitations)

For full details of base case and all sensitivity analyses, see appendix P.

Table 2: Monotherapy for adults with newly diagnosed focal epilepsy – Results of NCGC model

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
LTG	£8,841	8.8795		At £20K per QALY threshold, probability most cost-effective Base case: 82% All cheapest: 61% Cost of modified release CBZ: 52% Costs of generic LTG and Tegretol: 51%

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
				Improved tolerability of LEV: 82% LEV cost 50% and 70% reduced: 80% and 74% At £30K per QALY threshold: 74%
VPA	£9,291	8.8391	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 5% All cheapest: 1% Cost of modified release CBZ: 2% Costs of generic LTG and Tegretol: 0% Improved tolerability of LEV: 5% LEV cost 50% and 70% reduced: 5% and 4% LTG and CBZ unsuitable: 76% If LTG and CBZ unsuitable and LEV cost 50% and 70% reduced: 59% and 38% At £30K per QALY threshold: 4%
CBZ	£9,596	8.8797	£3,778,200 (ext dom)	At £20K per QALY threshold, probability most cost-effective Base case: 10% All cheapest: 37% Cost of modified release CBZ: 46% Costs of generic LTG and Tegretol: 48% Improved tolerability of LEV: 11% LEV cost 50% and 70% reduced: 9% and 7% At £30K per QALY threshold: 16%
GBP	£9,973	8.7958	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% All cheapest: 0% Cost of modified release CBZ: 0% Costs of generic LTG and Tegretol: 0% Improved tolerability of LEV: 0% LEV cost 50% and 70% reduced: 0% and 0% LTG and CBZ unsuitable: 2% If LTG and CBZ unsuitable and LEV cost 50% and 70% reduced: 1% and 1% At £30K per QALY threshold: 0%
OXC	£11,327	8.8933	£180,137	At £20K per QALY threshold, probability most cost-effective Base case: 2% All cheapest: 1% Cost of modified release CBZ: 1% Costs of generic LTG and Tegretol: 0% Improved tolerability of LEV: 2% LEV cost 50% and 70% reduced: 2% and 2% LTG and CBZ unsuitable: 21% If LTG and CBZ unsuitable and LEV cost 50% and 70% reduced: 16% and 12%

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
				At £30K per QALY threshold: 5%
TPM	£11,354	8.8288	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% All cheapest: 0% Cost of modified release CBZ: 0% Costs of generic LTG and Tegretol: 0% Improved tolerability of LEV: 0% LEV cost 50% and 70% reduced: 0% and 0% LTG and CBZ unsuitable: 1% If LTG and CBZ unsuitable and LEV cost 50% and 70% reduced: 0% and 0% At £30K per QALY threshold: 0 %
LEV	£12,187	8.8622	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% All cheapest: 0% Cost of modified release CBZ: 0% Costs of generic LTG and Tegretol: 0% Improved tolerability of LEV: 0% LEV cost 50% and 70% reduced: 3% and 13% LTG and CBZ unsuitable: 1% If LTG and CBZ unsuitable and LEV cost 50% and 70% reduced: 23% and 49% At £30K per QALY threshold: 0%

Evidence statements

Results of the base case found that lamotrigine was the most cost-effective AED for the first-line treatment of adults with newly diagnosed focal seizures. Lamotrigine 'dominated' gabapentin, levetiracetam, sodium valproate, and topiramate with lower costs and improved health outcomes (higher QALYs). This conclusion was robust to various sensitivity analyses.

In the base case, carbamazepine was ruled out through extended dominance, but in key sensitivity analyses around the costs of carbamazepine and lamotrigine, results indicated that carbamazepine may be the most cost-effective AED for the first-line treatment of adults with newly diagnosed focal seizures. There is some uncertainty in a decision between carbamazepine and lamotrigine.

Results of all analyses showed that oxcarbazepine was the most effective first-line AED, but that its additional cost compared to carbamazepine and lamotrigine was not justified by the additional benefit.

In circumstances where carbamazepine and lamotrigine are not suitable, sodium valproate or oxcarbazepine represent the next most cost-effective first-line AEDs for the treatment of newly diagnosed focal seizures. In the same scenario, levetiracetam may be considered cost-effective if its unit cost is reduced by 50%.

Marson 2007[161] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study detai

Table 3: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Marson 2007[161]

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
CBZ	£1,095	1.491		At £20K per QALY threshold, probability most cost-effective compared to: OXC: 17% TPM: 42% LTG: 41% GBP: 86%
OXC	£1,839	1.611	£6,200	At £20K per QALY threshold, 83% probability most cost-effective compared to CBZ
TPM	£1,930	1.541	Dominated	At £20K per QALY threshold, 58% probability most cost-effective compared to CBZ
LTG	£2,078 (a)	1.563	Dominated (b)	At £20K per QALY threshold, 59% probability most cost-effective compared to CBZ
GBP	£2,573	1.480	Dominated	At £20K per QALY threshold, 14% probability most cost-effective compared to CBZ

(a) Acquisition costs of LTG and TPM have decreased significantly since this evaluation was undertaken.
(b) In analysis of entire trial period and thus excluding oxcarbazepine from analysis, LTG is cost-effective compared to CBZ (£11,851 per QALY)

Evidence statements

Oxcarbazepine is the most cost-effective AED evaluated as monotherapy, less costly and more effective in terms of QALY gain than gabapentin, lamotrigine and topiramate. Oxcarbazepine is more costly and more effective in terms of QALYs gained than carbamazepine, with each additional QALY costing £6,200 (partially applicable and potentially serious limitations).

Carbamazepine is the least costly and second least effective AED in terms of QALY gain evaluated as monotherapy (partially applicable and potentially serious limitations).

Gabapentin is the most costly and least effective AED in terms of QALY gain evaluated as monotherapy (partially applicable and potentially serious limitations).

Lamotrigine and topiramate are more costly and less effective in terms of QALY gain than oxcarbazepine (partially applicable and potentially serious limitations).

When oxcarbazepine was excluded from the analysis in order to use data from the entire trial period, lamotrigine was the most cost-effective AED evaluated as monotherapy. Also, it is likely that if

current costs of lamotrigine were used, it would be cost-effective compared to alternative AEDs evaluated as monotherapy.

Marson 2007 [161] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Table 4: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Marson 2007[161]

AED	Total cost (£) per patient	Total effects (seizures)	ICER (£ / seizure avoided) (a)	Uncertainty
CBZ	£1,151	50.9		At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to: OXC: 15%, 10%, 10%, 9% TPM: 73%, 67%, 65%, 63% LTG: 59%, 52%, 50%, 48% GBP: 95%, 92%, 90%, 90%
OXC	£1,815	32.0	£35	At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ: 85%, 90%, 90%, 91%
TPM	£2,059	59.4	Dominated	At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ: 27%, 33%, 35%, 37%
LTG	£1,946 (b)	50.9	Dominated (c)	At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ: 41%, 48%, 50%, 52%
GBP	£2,594	85.3	Dominated	At £160, £400, £800 and £1600 per seizure avoided, probability most cost-effective compared to CBZ: 5%, 8%, 10%, 10%

(a) No willingness to pay threshold for seizures avoided exists.
(b) Acquisition costs of LTG and TPM have decreased significantly since this evaluation was undertaken.
(c) In analysis of entire trial period and thus excluding oxcarbazepine from analysis, LTG may be cost-effective compared to CBZ (£80 per seizure avoided)

Evidence statements

Oxcarbazepine would appear to be the most cost-effective AED evaluated as monotherapy, less costly and more effective in terms of total seizures experienced than gabapentin, lamotrigine and topiramate. Oxcarbazepine is more costly and more effective in terms of total seizures experienced than carbamazepine, with each additional seizure avoided costing £35 (partially applicable and potentially serious limitations). Without an explicit willingness to pay per seizure avoided threshold, it is indeterminable as to whether oxcarbazepine would be considered cost-effective compared to carbamazepine.

Patients taking gabapentin, lamotrigine and topiramate experienced more total seizures and incurred higher costs than patients taking carbamazepine or oxcarbazepine, indicating that these AEDs may not be cost-effective (partially applicable and potentially serious limitations).

Hawkins 2005[181] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Table 5: Monotherapy for adults with newly diagnosed focal epilepsy – Results of Hawkins 2005[181]

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
CBZ	£4,428	9.392		At £20K per QALY threshold, probability most cost-effective Base case: 42%
VPA	£4,572	9.404	£11,731	At £20K per QALY threshold, probability most cost-effective Base case: 46%
LTG	£6,133 (a)	9.382	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0%
OXC	£6,294	9.415	Extended Dominance	At £20K per QALY threshold, probability most cost-effective Base case: 12%
TPM	£7,838	9.430	£126,519	At £20K per QALY threshold, probability most cost-effective Base case: 0%

(a) Acquisition costs of LTG and TPM have decreased significantly since this evaluation was undertaken

Evidence statements

Sodium valproate is the most cost-effective AED evaluated as monotherapy given a threshold willingness to pay of £20,000 per QALY (partially applicable and potentially serious limitations).

Lamotrigine was the least effective among AEDs evaluated as monotherapy and was more costly than carbamazepine and sodium valproate (partially applicable and potentially serious limitations).

Oxcarbazepine and topiramate are not cost-effective compared to alternative AEDs evaluated as monotherapy (partially applicable and potentially serious limitations).

10.3.7 Monotherapy for children with newly diagnosed focal epilepsy

10.3.7.1 Matrix of the evidence for children

Placebo					
Carbamazepine					
Phenobarbital					
Lamotrigine		1[164]			
Phenytoin					

Valproate								
Oxcarbazepine					1[182]			
Vigabatrin		1[183]						
	Pla	CBZ	PHB	LTG	PHT	VPA	OXC	VGB

Placebo (Pla) Carbamazepine (CBZ) Phenobarbital (PHB) Lamotrigine (LTG)

Phenytoin (PHT) Sodium valproate (VPA) Oxcarbazepine (OXC) Vigabatrin (VGB)

Clobazam (CLB)

10.3.7.2 Lamotrigine versus Carbamazepine

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [184] of AEDs, including carbamazepine and lamotrigine, used as monotherapy in the treatment of children with newly diagnosed focal epilepsy was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as monotherapy in newly diagnosed children. This was based on clinical evidence from Nieto-Barerra 2001[164] and Guerreiro 1997[182]. The complete results of this study and the NCGC children monotherapy model are presented in section 10.3.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of seizure-free children. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more children taking lamotrigine monotherapy had an infection compared to children taking carbamazepine monotherapy, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY).

Significantly more children taking carbamazepine monotherapy experienced dizziness compared to children taking lamotrigine monotherapy. (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the proportion of children withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the incidence of the following adverse events:

- headache (VERY LOW QUALITY)
- pharyngitis (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed first line treatment with lamotrigine might be cost-effective compared to first line treatment with carbamazepine, but there was considerable uncertainty in this result (partially applicable and potentially serious limitations).

One economic evaluation based on a decision analytic model showed lamotrigine monotherapy to be more costly and less effective than carbamazepine monotherapy (directly applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.3.7.3 Oxcarbazepine versus phenytoin

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Adverse effects – statistically significant results

Significantly fewer participants on oxcarbazepine monotherapy withdrew due to adverse events compared to phenytoin monotherapy. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing oxcarbazepine and phenytoin in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes

- quality of life outcomes.

10.3.7.4 Vigabatrin versus carbamazepine

Clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the proportion of seizure free children. (VERY LOW QUALITY)

Adverse events– statistically non-significant results

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the proportion of children withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between vigabatrin monotherapy and carbamazapine monotherapy for the incidence of :

- irritability/excitability (VERY LOW QUALITY).
- weight increase (VERY LOW QUALITY).
- excessive sedation (VERY LOW QUALITY).
- urticarial rash (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing vigabatrin and carbamazepine in children with newly diagnosed focal epilepsy was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.3.8 Health economic evidence of AEDs used as monotherapy for children with newly diagnosed focal epilepsy

One study [184] assessing the cost-effectiveness of AEDs used as monotherapy was included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessment of the methodology and applicability. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as first-line monotherapy in

children with newly diagnosed focal epilepsy. This was based on clinical evidence from Nieto-Barrera 2001[164] and Guerreiro 1997[182]. See appendix R for full details and results of modelling.

Economic study characteristics

Table 6: Monotherapy for children with newly diagnosed focal epilepsy - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCGC Model – children monotherapy (see Appendix R for details)	Minor limitations	Directly applicable	Decision analytic model; comparators included carbamazepine, lamotrigine and oxcarbazepine; time horizon 15 years starting age 2 years; clinical data based on clinical review
Frew 2007[184]	Potentially serious limitations	Partially applicable	Patient simulation decision model; comparators for first-line monotherapy included standard drugs (CBZ, VPA and PHT) and LTG; time horizon varied between 3 months and 15 years.

Economic study results

NCGC Model – children monotherapy (directly applicable, minor limitations)

For full details of base case and all sensitivity analyses, see appendix R.

Table 7: Monotherapy for children with newly diagnosed focal epilepsy – Results of NCGC model

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
CBZ	£15,170	10.343		At £20K per QALY threshold, probability most cost-effective Base case: 86.74% Cohort starting age =10 yrs: 73.38% At £30K per QALY threshold: 86.72%
LTG	£15,612	10.251	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 12.16% Cohort starting age =10 yrs: 26.12% At £30K per QALY threshold: 11.88%
OXC	£16,467	10.183	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 1.1% Cohort starting age =10 yrs: 0.5% At £30K per QALY threshold: 1.4%

Evidence statements

Carbamazepine is the most effective and least costly among the AEDs evaluated as monotherapy in children with newly diagnosed focal epilepsy (directly applicable and minor limitations).

Lamotrigine and oxcarbazepine are more costly and less effective than carbamazepine (directly applicable and minor limitations).

Frew (2007)[184] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Table 8: Monotherapy for children with newly diagnosed focal epilepsy – Results of Frew 2007[184]

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
Baseline (no new AEDs)	Point estimates cannot be determined from the data provided			At £20K per QALY threshold, probability most cost-effective Base case: 60%
LTG (first line monotherapy)	Point estimates cannot be determined from the data provided		More costly and possibly more effective, but ICER cannot be determined from the data provided.	At £20K per QALY threshold, probability most cost-effective Base case: 40%

Evidence statements

In 40% of simulations, first line monotherapy with lamotrigine was optimal compared to a strategy involving only older drugs (carbamazepine, sodium valproate and/or phenytoin). Therefore, lamotrigine monotherapy may be cost-effective, but there is considerable uncertainty in this decision (partially applicable and potentially serious limitations). If current costs for lamotrigine were used, first line monotherapy with lamotrigine may be optimal in a greater proportion of simulations.

10.3.9 New recommendations and link to evidence

First-line treatment in children, young people and adults with newly diagnosed focal seizures

Recommendation	**85. Offer carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures. [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure freedom, withdrawal due to adverse events and time to treatment failure, time to first seizure and time to 12 month remission were the most clinically important outcomes for this recommendation.
Trade off between clinical benefits and harms	The efficacy at reducing seizures has to be balanced against the potential side effects for each of these drugs. Lamotrigine and carbamazepine were both found to have efficacy. Carbamazepine had a longer time to first seizure (in the meta-analysis of direct evidence and the IPD results) and there was no significant difference for seizure freedom. Lamotrigine has a better adverse events profile than carbamazepine. Lamotrigine requires slow titration to reduce risk of rash, which may make it unsuitable for individuals requiring rapid control. The meta-analysis of direct evidence found significantly more participants on carbamazepine compared to lamotrigine withdrew due to adverse

	events and the direct evidence and IPD results showed carbamazepine prolonged the time to first seizure and had a shorter time to withdrawal than lamotrigine. Oxcarbazepine has a similar adverse events profile and efficacy to carbamazepine and lamotrigine, except the IPD analysis found that oxcarbazepine had longer time to first seizure than lamotrigine. Whereas the direct evidence found no difference. Carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations. Carbamazepine had more efficacy than sodium valproate but sodium valproate showed no significant differences to oxcarbazepine. Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity. In children, lamotrigine and carbamazepine have similar efficacy and adverse events profiles, with the exception of incidence of dizziness which is more prominent with carbamazepine. Lamotrigine and oxcarbazepine had more efficacy (IPD results for time to withdrawal, but no difference in the direct evidence) and less adverse events than phenytoin. It should be noted that the IPD meta-analysis for lamotrigine versus phenytoin was based on indirect evidence. Phenytoin had no significant difference when compared to carbamazepine. Topiramate had similar efficacy to sodium valproate and oxcarbazepine. However phenytoin and topiramate have disadvantages due to drug interactions and their adverse events profiles. Gabapentin was less effective than other AEDs. Vigabatrin is not recommended because of its adverse effects in long-term use. Phenobarbital is not recommended because of adverse effects. Clobazam is not recommended because of concerns with tolerability. Therefore these drugs were not thought to be appropriate to recommend as first-line treatment.
Economic considerations	The GDG considered all relevant sources of economic evidence and various base case and sensitivity analyses from the original NCGC decision model when developing their recommendations for first line treatment of individuals with newly diagnosed focal seizures. The results of the NCGC analysis showed that health benefits in terms of QALYs gained are similar across the various AEDs and it showed that there are some differences in cost, particularly between drugs that are being produced and prescribed generically and those that are not. Because of its low acquisition cost and good tolerability, the analysis found that lamotrigine is likely to be the most cost effective AED. Results from the SANAD trial also found lamotrigine likely to be a cost-effective first line AED, and given reductions in its unit cost, it may be even more cost-effective now than when the trial was undertaken. Based on these results, the GDG felt that lamotrigine was likely to represent good value for NHS resources and should be offered to patients with newly

	diagnosed focal seizures who require treatment. In making their recommendations, the GDG also considered the results of a series of key sensitivity analyses which indicated that carbamazepine may be as cost effective as lamotrigine depending on the costing assumptions made. Because of this substantial uncertainty and given carbamazepine's current place in the care of people with focal seizures, the GDG believed it too should be an option for the first-line treatment of individuals with newly diagnosed focal seizures. Among children, the NCGC analysis showed that a strategy of offering carbamazepine as first-line treatment is likely to be most cost-effective, but that lamotrigine or oxcarbazepine might be cost-effective if carbamazepine were unsuitable. The GDG wished to guide health care professionals, patients and commissioners on cost-effective alternatives to lamotrigine and carbamazepine in the situation where these were considered unsuitable. To do this, they relied on the results of a sensitivity analysis in which lamotrigine and/or carbamazepine were removed from consideration. In such a scenario, sodium valproate was considered the most cost-effective alternative and for patients for whom sodium valproate too is inappropriate, oxcarbazepine is most likely to represent the best value for NHS resources. The estimation of oxcarbazepine's relative cost-effectiveness as a first line AED was different in the NCGC analysis compared to the findings of the SANAD trial. Both analyses found oxcarbazepine to be the most effective AED in terms of QALY gain, but where the SANAD trial found it to be cost effective, the NCGC analysis did not. The QALY difference between oxcarbazepine and carbamazepine measured in the SANAD trial was nearly 9 times larger than the same difference modelled by the NCGC analysis. Given the non-significant differences in terms of efficacy and tolerability between oxcarbazepine and carbamazepine found in the SANAD trial and used in the NCGC analysis it seems that there are benefits to treatment with oxcarbazepine not captured by the NCGC decision model. That said, it is unclear what benefits are driving the substantial QALY gain enjoyed by patients receiving oxcarbazepine in the SANAD trial over and above patients receiving other drugs, even lamotrigine. The QALY difference between oxcarbazepine and carbamazepine is more than twice the difference between lamotrigine and carbamazepine. The GDG considered the strengths and limitations of the two sources of economic evidence, particularly as they applied to conclusions about oxcarbazepine. A strength of a within-trial analysis like SANAD is that it is based on actual patient data; however, a limitation is that the same within-trial analysis is only based on that data and not the synthesis of all trial data across all comparators of interest. Another limitation is that the within-trial analysis from SANAD is based only on costs and QALYs measured over a 2-year time horizon, which is potentially too short when considering the management of a long-term condition like

	epilepsy. The NCGC model is not without limitations, but it was based on all the available evidence (including SANAD), thanks to a network meta-analysis undertaken by Tudur Smith and colleagues[38], included all the comparators relevant to the decision problem and used data and informed assumptions about the extrapolation of treatment effects up to 15 years. Without a clear understanding of exactly what is driving the difference between the SANAD trial results and the NCGC analysis results, the GDG was faced with a genuine uncertainty about the cost-effectiveness of oxcarbazepine. Given this uncertainty and the knowledge that the mean daily cost of oxcarbazepine is about 2 times that of carbamazepine and 5 times that of lamotrigine, the GDG decided to recommend oxcarbazepine as a reasonable alternative when neither of these two are suitable or when either is poorly tolerated. Informed by the evidence from Kwan and Brodie, the GDG assumed that the cost-effectiveness of different AEDs used as first-line monotherapy would hold true for their use as second-line monotherapy. For example, if lamotrigine was trialled and poorly tolerated and carbamazepine was unsuitable for any given reason, sodium valproate would represent the next most cost-effective choice (or oxcarbazepine if sodium valproate was inappropriate). Other AEDs licensed for use as monotherapy, including gabapentin, levetiracetam and topiramate, were not shown to be cost-effective at current 2011 prices. However non-proprietary levetiracetam is expected to come to market within the near future and its relative cost-effectiveness compared with the AEDs listed in this recommendation is sensitive to changes in unit cost. Because it is difficult to know not only how much the price of levetiracetam will drop with the introduction of generic competition, but also how much the cost of other AEDs may change as well, the GDG made recommendations for the treatment of newly diagnosed focal seizures based on current information. A subsequent recommendation provides additional information to users of the guideline regarding the circumstances under which levetiracetam is likely to be a cost-effective first line AED. Phenytoin was not considered in the economic analysis because it has a narrow therapeutic window.
Quality of evidence	In adults, the studies included in the evidence were of low quality due to serious limitations in the study design. Many of the studies were unblinded or had inadequate detailing of randomisation and allocation concealment with some of the studies having high dropout. One important study (the SANAD trial Marson, 2007 [41] was a large pragmatic trial which informed many of the comparisons. This was an unblinded multicentre study. In children, three studies were included (Nieto-Barrera, 2001[164], Guerreiro, 1997 and Zamponi 1999) the majority of which were unblinded with limitations.
Other considerations	The GDG found no evidence to refute the place of drugs listed as

	first-line in the original guideline. The only exception was for topiramate which has been advised as adjunctive therapy because it was not found to be cost effective in this analysis. Sodium valproate inhibits the metabolism of lamotrigine. This needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. The GDG considered that in practice there would be a concomitant increase in the lamotrigine dose. Oxcarbazepine and carbamazepine are hepatic enzyme-inducing drugs and may interact with other medications; this may influence the choice of AED in some individuals. The metabolism of lamotrigine may be increased by oestrogens in contraceptives. In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration. There is increased risk of side effects with carbamazepine in older people. Carbamazepine has been associated with a higher incidence of premature death in old people compared to lamotrigine. The GDG suggested the use of the controlled release preparation of carbamazepine and to use low doses and escalate very cautiously. Please refer to recommendations 80 and 253. Otherwise use an alternative first-line therapy in this population. It is better to use non-enzyme inducing AEDs as this population are likely to be taking other medications. During the literature review we identified an analysis of Individual Patient Data (IPD) which included data from eight IPD Cochrane reviews and data from the SANAD trial of eight different AEDs (carbamazepine, sodium valproate, phenytoin, phenobarbital, oxcarbazepine, lamotrigine) in monotherapy of focal seizures[38]. We used the IPD analysis as supplementary evidence to the direct evidence. The GDG considered the IPD analysis in the decision making process alongside the direct evidence. In relation to the findings, common results were found in our direct evidence and the IPD analysis[38]. In all analyses, no single drug was significantly more effective than carbamazepine for time to 12 months remission. The IPD analysis [38] found that sodium valproate was significantly less effective than carbamazepine in achieving time to 12 months remission and had a shorter time to first seizure. There was no direct evidence for this drug comparison. Other comparisons which had no direct evidence but had IPD results included phenytoin had a shorter time to treatment failure than oxcarbazepine or phenobarbital and a shorter time to first seizure than phenobarbital. Results which were non-significant for the direct evidence but significant for the IPD analysis included lamotrigine which had a shorter time to first seizure than topiramate or oxcarbazepine. The GDG considered that the difference in results for some comparisons originated from

	the different studies contributing to the direct evidence and the IPD analyses. Studies included in the IPD analyses were excluded from the direct evidence mainly on the basis that they did not meet the cut-off point for exclusion of seizure types and the age distribution. The GDG considered that different patients react differently to the different drugs and there may be a need to try different options to get the balance right between seizure freedom and adverse effects. If the first AED is ineffective, a second AED should be added alongside the initial AED and, if seizures are controlled, the first AED may be withdrawn, recognising that some patients will prefer to remain on two AEDs if seizure-free. The GDG considered that it is generally preferable to avoid polytherapy.

Recommendation	**86. Levetiracetam is not cost effective at June 2011 unit costs[z]. Offer levetiracetam, oxcarbazepine or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Be aware of the teratogenic risks of sodium valproate (see recommendation 83).[new 2012]**
Relative values of different outcomes	Seizure freedom, withdrawal due to adverse events and withdrawal due to lack of efficacy were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Although both levetiracetam and carbamazepine controlled-release had very similar findings in terms of efficacy, levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine controlled-release which is why it was not recommended as the drug of first choice. However it may be useful for people in whom other first line AEDs are not suitable. Oxcarbazepine has a similar adverse events profile and efficacy to carbamazepine and lamotrigine, except the IPD analysis found that oxcarbazepine had longer time to first seizure than lamotrigine. Whereas the direct evidence found no difference. Carbamazepine had more efficacy than sodium valproate and sodium valproate showed no significant differences to oxcarbazepine. Sodium valproate would not be a first choice in females of present or future child-bearing potential, because of increased risks of

[z] Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. Cost taken from the National Health Service Drug Tariff for England and Wales, available at www.ppa.org.uk/ppa/edt_intro.htm

	teratogenicity. The GDG considered that levetiracetam lacks interaction with other drugs.
Economic considerations	The GDG considered the results of the NCGC cost-effectiveness analysis, in which some AEDs licensed for use as monotherapy, including gabapentin, levetiracetam and topiramate, were not shown to be cost-effective at current 2011 prices. Given the current use of levetiracetam in clinical practice and the imminent arrival of generic products to the market the GDG considered it important to provide additional information to users of the guideline regarding the circumstances under which levetiracetam is likely to be a cost-effective first line AED. The analyses showed that there is quite a bit of uncertainty around the cost-effectiveness of levetiracetam, driven by a limited clinical evidence base and questions about its future cost. Lamotrigine was found to be more cost effective than levetiracetam, and this result was consistent across a range of sensitivity analyses (dominating levetiracetam in some and representing better value for money given the NICE threshold in others). Carbamazepine was also more cost effective than levetiracetam, except when levetiracetam was assumed to be more tolerable than carbamazepine and 70 percent less costly than it is currently. The GDG next considered the situation wherein carbamazepine and lamotrigine are considered unsuitable or have been poorly tolerated. Based on the interpretation of the evidence, the GDG recommended that sodium valproate and oxcarbazepine are considered in this group. The sensitivity analysis around cost was undertaken for this clinical scenario as well, and found the probability of levetiracetam being considered cost-effective relative to sodium valproate and oxcarbazepine improves as price decreases. A 50 percent price decrease makes levetiracetam more cost effective than oxcarbazepine but not cost effective compared to sodium valproate. However, if levetiracetam is more tolerable than carbamazepine, then a 50 percent price decrease makes levetiracetam cost-effective compared to both drugs, although substantial uncertainty surrounds this conclusion. When all recommended first-line AEDs (carbamazepine, lamotrigine, oxcarbazepine and sodium valproate) are removed from the analysis due to contraindications, gabapentin is the AED most likely to be considered cost-effective. However, if the future acquisition cost of levetiracetam is 20 to 30 percent less than what it is currently, then levetiracetam becomes the most cost-effective AED given the NICE willingness to pay threshold. The GDG considered this scenario and concluded that in the situation where all recommended first line drugs are contraindicated or unsuitable, there is a likelihood that gabapentin and topiramate might not be appropriate either, thus lending further weight to the choice of levetiracetam even at current costs. With the expectation that a modest drop in its price will move it from marginally not cost-

	effective to most cost-effective, the GDG decided it should be offered in preference to gabapentin in this clinical situation. The GDG considered the uncertainties around levetiracetam driving the results of the base case and various sensitivity analyses. They also accepted that they did not know not only how much the price of levetiracetam will drop with the introduction of generic competition, nor how much the cost of other AEDs might change as well. After careful consideration, the GDG determined that levetiracetam should be offered as a first-line treatment under two circumstances. Firstly, in the circumstance when all the recommended first-line treatments (carbamazepine, lamotrigine, oxcarbazepine and sodium valproate) are unsuitable. Secondly, as an alternative to oxcarbazapine and sodium valproate (when carbamazepine and lamotrigine are unsuitable, poorly tolerated or ineffective), if levetiracetam can be acquired for a cost at least 50 percent less than June 2011 unit costs. The GDG felt that this recommendation and the detail include therein, would clearly outline the conditions under which treatment with levetiracetam would represent a cost-effective use of limited NHS resources.
Quality of evidence	In adults, the studies included in the evidence were of low quality due to serious limitations in the study design. Many of the studies were unblinded or had inadequate detailing of randomisation and allocation concealment with some of the studies having high dropout. One important study (the SANAD trial Marson, 2007 [41] was a large pragmatic trial which informed many of the comparisons. This was an unblinded multicentre study. In children, one study included oxcarbazepine (Guerreiro, 1997) which had serious limitations. One trial with high dropout rates in both arms showed there was no significant difference between levetiracetam and carbamazepine in the proportion of seizure free participants and withdrawal due to adverse events. However, significantly higher proportion of participants on levetiracetam withdrew due to lack of efficacy compared to carbamazepine. This is partly a GDG consensus opinion based recommendation.
Other considerations	Levetiracetam is only licensed for people over 16 year olds. It is useful because it does not interact with hormonal contraception. The GDG opinion was that the limited evidence currently available suggests that levetiracetam does not carry an increased risk of teratogenicity. Sodium valproate inhibits the metabolism of lamotrigine. This needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. The GDG considered that in practice there would be a concomitant increase in the lamotrigine dose. Oxcarbazepine is a hepatic enzyme-inducing drug and may interact with other medications; this may influence the choice of AED in some individuals.

	In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration. During the literature review we identified an analysis of Individual Patient Data (IPD) which included data from eight IPD Cochrane reviews and data from the SANAD trial of eight different AEDs (carbamazepine, sodium valproate, phenytoin, phenobarbital, oxcarbazepine, lamotrigine) in monotherapy of focal seizures[38]. We used the IPD analysis as supplementary evidence to the direct evidence. The GDG considered the IPD analysis in the decision making process alongside the direct evidence. In relation to the findings, common results were found in our direct evidence and the IPD analysis[38]. In all analyses, no single drug was significantly more effective than carbamazepine for time to 12 months remission. The IPD analysis [38] found that sodium valproate was significantly less effective than carbamazepine in achieving time to 12 months remission and had a shorter time to first seizure. There was no direct evidence for this drug comparison. Other comparisons which had no direct evidence but had IPD results included phenytoin had a shorter time to treatment failure than oxcarbazepine or phenobarbital and a shorter time to first seizure than phenobarbital. Results which were non-significant for the direct evidence but significant for the IPD analysis included lamotrigine which had a shorter time to first seizure than topiramate or oxcarbazepine. The GDG considered that the difference in results for some comparisons originated from the different studies contributing to the direct evidence and the IPD analyses. Studies included in the IPD analyses were excluded from the direct evidence mainly on the basis that they did not meet the cut-off point for exclusion of seizure types and the age distribution. The GDG considered that different patients react differently to the different drugs and there may be a need to try different options may need to be tried to get the balance right between seizure freedom and adverse effects. If the first AED is ineffective, a second AED should be added alongside the initial AED and, if seizures are controlled, the first AED may be withdrawn, recognising that some patients will prefer to remain on two AEDs if seizure-free. The GDG considered that it is generally preferable to avoid polytherapy.

Recommendation	**87. Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 85 and 86). [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure freedom, withdrawal due to adverse events and time to treatment failure, time to first

	seizure and time to 12 month remission were the most clinically important outcomes for this recommendation.
Trade off between clinical benefits and harms	Phenytoin had less efficacy and more adverse events than lamotrigine, oxcarbazepine and no significant difference compared to carbamazepine. Topiramate had similar efficacy to sodium valproate and oxcarbazepine. However phenytoin and topiramate have disadvantages due to drug interactions and their adverse events profiles. Gabapentin was less effective than other AEDs. Vigabatrin is not recommended because of its adverse effects in long-term use. Phenobarbital is not recommended because of adverse effects. Clobazam is not recommended because of concerns with tolerability. Therefore these drugs were not thought to be appropriate to recommend as first-line treatment. Levetiracetam and carbamazepine controlled-release had very similar findings in terms of efficacy, but levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine controlled-release which is why it was not recommended as the drug of first choice. However the GDG considered it to be useful for people in whom other first line AEDs are not suitable and that levetiracetam lacks interaction with other drugs. The GDG considered that the five AEDs (lamotrigine, carbamazepine, oxcarbazepine, sodium valproate and levetiracetam) offered as first line treatment in newly diagnosed focal seizures may have instances where they are tolerated but are not effective. Therefore due to the concerns with the other AEDs, the GDG agreed that in these cases adjunctive treatment should be considered.
Economic considerations	The original cost-effectiveness analysis undertaken for the guideline indicates that the AEDs used as adjunctive therapy for refractory focal seizures were more effective and more costly than continuing patients on monotherapy. However, adjunctive therapy with a subset of AEDs may be cost-effective at the NICE threshold of £20,000 per QALY. There is considerable uncertainty as to which AED represents the optimal use of NHS resources as much depends on what is appropriate for the individual patient and on his/her previous treatment history.
Quality of evidence	This recommendation was based on the clinical expertise of the GDG and via consensus and the evidence base from adjunctive treatment of refractory focal seizures which included placebo-controlled trials which showed it was better to have any treatment than no treatment.
Other considerations	Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity. Sodium valproate inhibits metabolism of lamotrigine. This needs to

	be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be concomitant increase in the lamotrigine dose. Oxcarbazepine and carbamazepine are hepatic enzyme-inducing drugs and may interact with other medications; this may influence the choice of AED in some individuals. The metabolism of lamotrigine may be increased by oestrogens in contraceptives. In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration. There is increased risk of side effects with carbamazepine in older people. Carbamazepine has been associated with a higher incidence of premature death in old people compared to lamotrigine. The GDG suggested the use of the controlled release preparation of carbamazepine and to use low doses and escalate very cautiously. Otherwise use an alternative first-line therapy in this population. It is better to use non-enzyme inducing AEDs as this population are likely to be taking other medications.

10.3.10 New research recommendations (for full list see section 2.11)

10.3.10.1 Newly diagnosed seizures (focal & generalised) – monotherapy

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

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

Why this is important

Levetiracetam and other AEDs licensed for the treatment of focal and generalised seizures since publication of the original guideline 'The epilepsies' (NICE clinical guideline 20) in 2004 have not been evaluated as first-line monotherapy.

The research should include:

- a prospective randomised controlled trial
- all age groups
- subgroup analyses on seizure types and syndromes
- primary outcome of seizure freedom
- secondary outcomes, including seizure reduction, quality of life and cognitive outcome
- an attempt to obtain data on pharmaco-resistance.

10.4 Therapy for refractory focal seizures

10.4.1 Introduction

Focal seizures, as stated in the previous section, originate from one area of the brain. They are the most common seizure type in adults and children. Although seizure freedom remains the goal of therapy, in this population optimal seizure control may be more achievable. Treatment success has been most recently defined by the ILAE as a seizure free duration that is at least three times the longest seizure free interval prior to starting the new treatment with a sustained response over 12m (Kwan et al 2009)[185].

Recent EMA[aa] decisions regarding licensing of AEDS for use in children indicate that for 'focal epilepsies especially cryptogenic and symptomatic, and idiopathic generalised epilepsies, with absences, myoclonic and/or generalised convulsive seizures, (…) the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established.' As a result of this, and with the agreement of the GDG we have combined data for adults and children in the refractory focal seizures review.

10.4.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with refractory focal seizures. For studies in which both focal and primary generalised seizures were combined, a 20% threshold was used as a threshold for "contamination" for the outcome of seizure freedom and a 50% threshold for the outcomes of adverse events.

10.4.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for epilepsy in adults with refractory focal epilepsy. The interventions we included in our search were; eslicarbazepine acetate, pregabalin, zonisamide, lacosamide, lamotrigine, gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbital, felbamate, clobazam, clonazepam, acetazolamide, primidone, sodium valproate, sulthiame and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Single AED therapy for refractory focal seizures

Placebo				
Lamotrigine				
Tiagabine	1[186]			
Oxcarbazepine	1[187]			

aa http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070043.pdf

Sodium valproate		1[188]				
	PLA	LTG	TGB	OXC	VPA	

Adjunctive AED therapy for refractory focal seizures

Placebo																
Carbamazepine																
Clobazam	1[189]															
Eslicarbazepine acetate	4[190-193]															
Felbamate	1[194]															
Gabapentin	6[195-199, 200]															
Lacosamide	3[201,202, 203]															
Lamotrigine	12[204-213, 214, 215]					1[216]										
Lamotrigine XR	1[217]															
Levetiracetam	12[218-225, 226, 227, 228, 229]							1[230]								
Levetiracetam XR	1[231]															
Oxcarbazepine	2[232, 233]															
Phenytoin																
Pregabalin	6[234-238, 215]							1[215]								
Sodium valproate	1[239]					1[240]										
Topiramate	11[239,241-248, 249, 250]							1[251]							2[239,252]	

Tiagabine	4[253-256]	1[257,258]						1[259]					2[257,258]				
Vigabatrin	9[206,260-263,264-266, 267]					1[268]											
Zonisamide	5[269-272, 273]																
Primidone															1[274]		
	PLC	CBZ	CLB	ECBZ	FBM	GBP	LAC	LTG	LTG-XR	LEV	LEV-XR	OXC	PHT	PGB	VPA	TPM	TGB

Placebo (PLA) Clobazam (ClB) Eslicarbazepine acetate (ECBZ) Felbamate(FBMl) Gabapentin (GBP) Lacosamide(LAC) Lamotrigine (LTG) Lamotrigine XR (LTG-XR)
Levetiracetam (LEV) Levetiracetam XR (LEV-XR) Oxcarbazepine (OXC) Topiramate (TPM) Tiagabine (TGB) Vigabatrin (VGB) Zonisamide(Zon)

10.4.4 Single AED therapy for refractory focal seizures

10.4.4.1 Lamotrigine versus sodium valproate

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of lamotrigine, sodium valproate and carbamazepine as monotherapy in the treatment of adults with refractory focal epilepsy was identified in the economic literature search. The results of this study are presented in full in section 10.4.5.

Evidence statements

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the incidence of headache. (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed lamotrigine monotherapy to be more costly and equally effective as sodium valproate monotherapy in a population with refractory focal epilepsy (partially applicable and very serious limitations). In this analysis, carbamazepine monotherapy was less costly and more effective than both sodium valproate and lamotrigine.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.4.2 Tiagabine versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between tiagabine monotherapy and placebo for the proportion of participants withdrawn due to lack of efficacy. (VERY LOW QUALITY)

Adverse events– statistically non-significant results

No significant difference between tiagabine monotherapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between tiagabine monotherapy and placebo for the incidence of the following adverse events:

- dizziness (VERY LOW QUALITY)
- abnormal thinking (difficulty in concentration) (VERY LOW QUALITY)
- insomnia (VERY LOW QUALITY)
- paresthesia (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- amnesia (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing tiagabine monotherapy to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.4.3 Oxcarbazepine versus placebo

Direct clinical evidence

For details on the direct clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on oxcarbazepine monotherapy experienced seizure freedom compared to placebo, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Time to meeting exit/withdrawal of allocated treatment (time to meet one of the exit criteria) occurred significantly less rapidly in participants taking placebo monotherapy compared to participants taking oxcarbazepine monotherapy. (LOW QUALITY)

Adverse events– statistically non-significant results

No significant difference between oxcarbazepine monotherapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and placebo for the incidence of the following adverse events:

- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- vomiting (VERY LOW QUALITY)
- pruritis (VERY LOW QUALITY)
- diplopia (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing oxcarbazepine monotherapy to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.5 Health Economic Evidence for single AED therapy for refractory focal seizures

One study[181] assessing the cost-effectiveness of AEDs used as monotherapy in adults with refractory focal epilepsy was included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability.

Economic study characteristics

Table 9: Therapy in adults with refractory focal epilepsy - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Hawkins (2005)[181]	Potentially serious limitations (a)	Partially applicable (b,c)	Decision analytic model; comparators included carbamazepine sodium valproate and lamotrigine; time horizon

Study	Limitations	Applicability	Other Comments
			15 years; clinical data based on network meta-analysis of data from Gilliam 1998 [188] and Kerr 2001[275]

(a) Unit costs of interventions are from 2002/03 and since then lamotrigine has come off patent and the non-proprietary price is dramatically lower.

(b) Effectiveness data was derived from a network meta-analysis that included at least one unpublished study that was not reviewed as part of our systematic review.

(c) Costs discounted at 6% per annum; QALYs discounted at 1.5% per annum.

Economic study results

Hawkins 2005[181] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for details.

Table 10: Single AED therapy in refractory focal seizures - Economic summary of findings – Hawkins 2005[181]

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
CBZ	£5,599	8.865		At £20K per QALY threshold, probability most cost-effective Base case: 79%
VPA	£5,728	8.856	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 21%
LTG	£6,749	8.856	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0%

Evidence statements

Cost-effectiveness

One economic evaluation based on a decision analytic model showed carbamazepine to be the most effective and least costly, and therefore most cost-effective AED used in the treatment of refractory focal seizures. The same analysis shows lamotrigine and sodium valproate therapynot to be cost-effective. This evidence is partially applicable and has very serious limitations.

10.4.6 Adjunctive therapy in children, young people and adults with refractory focal seizures

10.4.6.1 Lamotrigine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the

economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on lamotrigine adjunctive therapy compared to placebo had at least a 50% reduction in seizure frequency. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for seizure freedom (VERY LOW QUALITY).

No significant difference between lamotrigine adjunctive therapy and placebo for withdrawal due to lack of efficacy (LOW QUALITY).

Adverse events – statistically significant results

Significantly more participants on lamotrigine adjunctive therapy compared to placebo withdrew due to adverse events. (MODERATE QUALITY)

Significantly more participants on lamotrigine adjunctive therapy compared to placebo had an incidence of:

- dizziness (LOW QUALITY)
- diplopia (LOW QUALITY)
- ataxia (MODERATE QUALITY)
- blurred vision (MODERATE QUALITY)
- nausea (MODERATE QUALITY)
- somnolence (MODERATE QUALITY)
- vomiting, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- pain (LOW QUALITY)
- vertigo (MODERATE QUALITY)
- tremor, although there is uncertainty over the magnitude of its clinical effect (MODERATE QUALITY)

Significantly more participants on placebo compared to lamotrigine adjunctive therapy had an incidence of respiratory disorder (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for the incidence of the following adverse events:

- headache (LOW QUALITY)
- rash (VERY LOW)
- drowsiness (VERY LOW)
- faintness (VERY LOW)
- dyspepsia (VERY LOW)

- nasal congestion (VERY LOW)
- fatigue (VERY LOW)
- flushing (VERY LOW)
- co-ordination abnormality (VERY LOW)
- asthenia (VERY LOW)
- vision abnormality (VERY LOW)
- rhinitis (VERY LOW)
- tiredness (VERY LOW)
- accidental injury (VERY LOW)
- infection (LOW QUALITY)
- diarrhoea (LOW QUALITY)
- fever (LOW QUALITY)
- abdominal pain (LOW QUALITY)
- otitis media (LOW QUALITY)
- pharyngitis (LOW QUALITY)
- death (VERY LOW)
- aggravation of seizures (VERY LOW)

Quality of Life outcomes – statistically significant

Significantly more participants in the lamotrigine adjunctive therapy group compared to the placebo group had higher scores in the following psychological domain tests:

- happiness
- mastery

Quality of Life outcomes – statistically non-significant results

There is no significant difference between lamotrigine adjunctive therapy and placebo the following aspects of health related quality of life:

- physical
- social
- psychological

Cognitive outcomes – statistically non-significant results

There is no significant difference between lamotrigine adjunctive therapy and placebo for the following cognitive tests:

- Stroop test
- Leeds Psychomotor test
- Number cancellation test

Cost-effectiveness

Available economic evidence indicates that in the treatment of children, young people and adults, adjunctive lamotrigine is cost-effective compared to placebo.

- A cost-effectiveness analysis undertaken for the guideline showed that among adults, the addition of lamotrigine was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an expected incremental cost-

effectiveness ratio of £7,507. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

- A published cost-effectiveness analysis by Hawkins and colleagues also found that among adults, lamotrigine was cost-effective compared to placebo, but found that it was extendedly dominated by adjunctive oxcarbazepine. However, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that among children, the addition of lamotrigine was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £5,717 per QALY. This conclusion was consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, oxcarbazepine extendedly dominates lamotrigine and is the most cost effective adjunctive AED for children given a willingness to pay threshold of £20,000 per QALY gained (directly applicable and minor limitations).
- A published cost-effectiveness by Frew and colleagues found that there was too much uncertainty to reach a definitive conclusion about the relative cost effectiveness of any particular adjunctive AED strategy (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission

10.4.6.2 Lamotrigine extended release versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Lamotrigine extended-release was not included in the original economic model as it is not currently available in the UK.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on lamotrigine extended-release adjunctive therapy were seizure free than the placebo. (MODERATE QUALITY)

Significantly more participants on lamotrigine extended-release adjunctive therapy than the placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)

Adverse events – statistically significant results

Significantly more participants on lamotrigine extended-release adjunctive therapy withdrew due to adverse events compared to those taking placebo, although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly more participants in the lamotrigine extended-release adjunctive therapy than the placebo experienced dizziness. (MODERATE QUALITY)

Significantly fewer participants in the lamotrigine extended-release adjunctive therapy experienced nasopharyngitis than the placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine extended-release adjunctive therapy and placebo for the incidence of headache. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine extended-release adjunctive therapy to placebo was identified. However, the economic evidence for normal-release formulation lamotrigine indicates that it is cost-effective when compared with placebo. The cost effectiveness of extended-release formulation lamotrigine is dependent on how much more it might cost than normal-release formulation lamotrigine and whether it is equally effective and more or less tolerable.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.3 Lamotrigine versus levetiracetam

Clinical evidence

For details of the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation[181] of AEDs, including lamotrigine and levetiracetam, used as adjunctive therapy in the treatment of adults with refractory focal seizures was identified in the economic literature search. No studies comparing these AEDs in the treatment of children and young people were identified. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of this study and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for the incidence of:

- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and levetiracetam adjunctive therapy for incidence of death. (VERY LOW QUALITY)

Cognitive events and quality of life – statistically significant results

There was a significant improvement in Profile of Mood States (POMS) anger-hostility subscale and family/friend completed measure of depressive symptoms for lamotrigine adjunctive relative to levetiracetam adjunctive therapy.

There was a significant improvement in IDAS scales of irritability and anxiety for lamotrigine adjunctive therapy compared to levetiracetam adjunctive therapy.

There was a significant improvement in IDAS scale of depression for levetiracetam adjunctive therapy compared to lamotrigine adjunctive therapy.

Cognitive events and quality of life – statistically non-significant results

No significant improvements for lamotrigine adjunctive relative to levetiracetam adjunctive at end of maintenance period for most of the subscales including:

- POMS total mood disturbance, depression-dejection, vigor-activity, fatigue-inertia, confusion-bewilderment and tension-anxiety subscales.
- NDDI-E patient-completed measure of depressive symptoms
- ESS daytime sleepiness measure
- STAXI measure of the experience, expression, and control of anger
- BDI-II measure of severity of depressive symptoms.

Cost-effectiveness

Available economic evidence indicates that adjunctive levetiracetam is not cost-effective compared to adjunctive lamotrigine.

- One published cost-effectiveness analysis by Hawkins and colleagues showed adjunctive levetiracetam to be more costly and more effective than adjunctive lamotrigine, but had incremental cost-effectiveness ratios that exceeded the NICE willingness to pay threshold of £20,000 per QALY gained. However, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- Results of the cost-effectiveness analyses undertaken for the guideline also showed that in the treatment of children, young people and adults, given the current 2011 cost of levetiracetam, adjunctive levetiracetam was more costly and more effective than adjunctive lamotrigine.
    - Among adults, the incremental cost-effectiveness ratio for levetiracetam was £33,192. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).
    - Among children, the incremental cost-effectiveness ratio for levetiracetam was £24,503. This conclusion is consistent across a range of sensitivity analyses (directly applicable and minor limitations).

- Results of the guideline anlyses indicated that only if levetiracetam can be acquired for at least 30 percent less than its current 2011 unit cost is it potentially cost effective when compared with lamotrigine.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission

10.4.6.4 Lamotrigine versus tiagabine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs, including lamotrigine and tiagabine, used as adjunctive therapy in the treatment of adults with refractory focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and tiagabine adjunctive therapy for seizure freedom (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and tiagabine adjunctive therapy for 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and tiagabine therapy for incidence of:

- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- disturbed sleep (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- nervousness (VERY LOW QUALITY)
- paresthesia (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that adjunctive tiagabine is not cost effective when compared to lamotrigine.

- One published evaluation found that lamotrigine dominated tiagabine; that is, treatment with adjunctive lamotrigine was associated with lower costs and better health outcomes (higher QALYs) than treatment with adjunctive tiagabine (partially applicable and potentially serious limitations).
- The cost-effectiveness analysis developed for the guideline found that adjunctive tiagabine was more costly and more effective than adjunctive lamotrigine, but with an unacceptably high incremental cost-effectiveness ratio of £131,882 per QALY. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.5 Lamotrigine versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on topiramate adjunctive therapy than lamotrigine adjunctive therapy experienced seizure freedom, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on topiramate adjunctive therapy compared to lamotrigine adjunctive therapy had an incidence of headache, although there is uncertainty in the magnitude of its clinical effect. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for the incidence of

- dizziness (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results

Lamotrigine adjunctive therapy had significantly better scores compared to topiramate adjunctive therapy for:

- COWA
- POL test total overall score
- combined cognitive scores

Topiramate adjunctive therapy had significantly better scores compared to lamotrigine adjunctive therapy for:

- Stroop colour-word interference
- Symbol digit modalities (correct number)

Cognitive outcomes –statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and topiramate adjunctive therapy for:

- RAVLT delayed recall
- Lafayette grooved pegboard
- Digit cancellation test

Cost-effectiveness

Available economic evidence indicates that adjunctive topiramate may be cost-effective compared to lamotrigine, but there is uncertainty in this conclusion.

- Results from one published evaluation found that topiramate was more costly and more effective that lamotrigine, with an incremental cost-effectiveness ratio of £35,484 per QALY. However, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- The cost-effectiveness analysis developed for the guideline also found that adjunctive topiramate was more costly and more effective than adjunctive lamotrigine, but that the incremental cost-effectiveness ratio varied depending on assumptions made. The base case showed the ICER to exceed the NICE willingness to pay threshold of £20,000, but in sensitivity analyses where a larger proportion of patients were assumed to achieve seizure freedom from treatment, the ICER came down to £16,569. Similarly, when the lowest acquisition cost of all drugs was used, the ICER dropped further to £12,026 (directly applicable and minor limitations).
- A published cost-effectiveness by Frew and colleagues found that there was too much uncertainty to reach a definitive conclusion about the relative cost effectiveness of any particular adjunctive AED strategy (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure

- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- quality of life outcomes

10.4.6.6 Levetiracetam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs, including levetiracetam and placebo, used as adjunctive therapy in the treatment of adults with refractory focal seizures was identified in the economic literature search. No studies comparing these AEDs in the treatment of children and young people were identified. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of this study and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on levetiracetam adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (LOW QUALITY)

Significantly more participants on levetiracetam adjunctive therapy than placebo experienced seizure freedom. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on levetiracetam adjunctive therapy than the placebo had higher incidence of:

- infection (MODERATE QUALITY)
- somnolence (MODERATE QUALITY)
- asthenia (MODERATE QUALITY)

Significantly more participants on placebo than levetiracetam adjunctive therapy had higher incidence of aggravation of seizures (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy and placebo for withdrawal due to adverse events (VERY LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy and placebo for incidence of:

- abdominal pain (VERY LOW QUALITY)
- alanine aminotransferase (VERY LOW QUALITY)

- aspartate aminotransferase (VERY LOW QUALITY)
- decreases in platelets (VERY LOW QUALITY)
- decreases in white blood cells (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- agitation (VERY LOW QUALITY)
- nasopharyngitis (VERY LOW QUALITY)
- accidental injury (VERY LOW QUALITY)
- diarrhoea (VERY LOW QUALITY)
- flu (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- pain (VERY LOW QUALITY)
- rhinitis (LOW QUALITY)
- vomiting (VERY LOW QUALITY)
- anorexia (LOW QUALITY)
- hostility (LOW QUALITY)
- increased cough (LOW QUALITY)
- upper respiratory infection (VERY LOW QUALITY)
- aggression (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- psychomotor hyperactivity (VERY LOW QUALITY)
- irritability (VERY LOW QUALITY)
- incidence of somnolence (VERY LOW QUALITY)
- death (VERY LOW QUALITY)

Quality of life outcomes – statistically significant results

Participants in levetiracetam (1000mg and 3000mg) adjunctive group had significant improvement in mean scores compared to placebo on the following QOLIE-31 measures:

- seizure worry
- overall QoL
- cognitive functioning
- total score
- social function

Cognitive outcomes – statistically significant results

Participants in the levetiracetam group worsened whereas placebo patients improved on the aggressive behaviour score.

Cognitive outcomes – statistically non-significant results

Participants in levetiracetam (1000mg and 3000mg) adjunctive group had no significant improvement in mean scores compared to placebo on the following QOLIE-31 measures:

- Emotional well-being
- Energy-fatigue
- Medication effects

- Health status

Participants in levetiracetam adjunctive group had no difference in mean scores changes compared to placebo on the following cognitive measures:

- WFAML-2 change of general memory, visual memory, verbal memory, attention/concentration.
- Leiter-R ERS change in the cognitive/social and emotions/regulations domains
- CHQ-PF50 Social-emotional/behavioural/behaviour/mental health and psychosocial scores.

Cost-effectiveness

Available economic evidence indicates that in the treatment of children and adults, adjunctive levetiracetam may be cost-effective compared to placebo.

- A cost-effectiveness analysis undertaken for the guideline showed that among adults, the addition of levetiracetam was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an expected incremental cost-effectiveness ratio of £18,731 per QALY. This conclusion was consistent across a range of sensitivity analyses. However, when all relevant comparators, at June 2011 costs, were evaluated together, adjunctive oxcarbazepine and lamotrigine were likely to represent more cost-effective uses of NHS resources (directly applicable and minor limitations).
  - Only if levetiracetam can be acquired for at least 30 percent less than its current 2011 unit cost did it dominate oxcarbazepine and was it found to be potentially cost effective compared with lamotrigine.
- One published analysis by Hawkins and colleagues found that levetiracetam was more costly and more effective at an incremental cost-effectiveness ratio exceending the NICE willingness to pay threshold; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that among children, the addition of levetiracetam was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £14,286 per QALY. This conclusion is consistent across a range of sensitivity analyses. However, when all relevant comparators, at June 2011 costs, were evaluated together, adjunctive oxcarbazepine and lamotrigine were likely to represent more cost-effective uses of NHS resources (directly applicable and minor limitations).
  - Only if levetiracetam can be acquired for at least 40 percent less than its current 2011 unit cost did it dominate oxcarbazepine and was it found to be cost effective compared with lamotrigine.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission

10.4.6.7 Levetiracetam extended-release versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Levetiracetam extended-release was not included in the original economic model as it is not currently available in the UK.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on levetiracetam adjunctive therapy (extended-release) than placebo experienced seizure freedom, although there is uncertainty over the magnitude of its clinical effect. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy (extended release) and placebo for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (MODERATE QUALITY)

No significant difference between levetiracetam adjunctive therapy (extended-release) and placebo for the proportion of participants having treatment withdrawn due to lack of efficacy. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy (extended-release) and placebo for the proportion of participants having treatment withdrawn due to adverse events. (LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy (extended-release) and placebo for the incidence of headache. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing extended-release levetiracetam adjunctive therapy to placebo was identified. However, the economic evidence for normal-release formulation levetiracetam indicates that it is cost-effective when compared with placebo. The cost effectiveness of extended-release formulation levetiracetam is dependent on how much more it might cost than normal-release formulation levetiracetam and whether it is equally effective and more or less tolerable. Note that when all relevant comparators were evaluated together in the NCGC analysis, adjunctive oxcarbazepine and lamotrigine were likely to represent more cost-effective use of NHS resources.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- quality of life outcomes
- cognitive outcomes

10.4.6.8 Topiramate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on topiramate adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)

Significantly more participants on topiramate adjunctive therapy than placebo experienced seizure freedom. (MODERATE QUALITY)

Efficacy- statistically non- significant results

No significant difference was found between topiramate adjunctive therapy and placebo for the proportion of participants withdrawn due to lack of efficacy (VERY LOW QUALITY).

Adverse events – statistically significant results

Significantly more participants on topiramate adjunctive therapy than placebo withdrew due to adverse events. (MODERATE QUALITY)

Significantly more participants on topiramate adjunctive therapy than placebo experienced an incidence of:

- anorexia (MODERATE QUALITY)
- abdominal discomfort/pain, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- dizziness (LOW QUALITY)
- somnolence (LOW QUALITY)
- confusion, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- weight decrease (VERY LOW QUALITY)
- fatigue (LOW QUALITY)
- impaired concentration, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- abnormal thinking, although there is uncertainty in the magnitude of its clinical effect (VERY LOW QUALITY)
- ataxia (LOW QUALITY)
- paraesthesia, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- emotional lability (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo for the incidence of:

- nausea/vomiting (VERY LOW)
- headache (VERY LOW)
- amblyopia (VERY LOW)
- dizziness/somnolence (VERY LOW)
- speech disorder (VERY LOW)
- aphasia (VERY LOW)
- abnormal vision (VERY LOW)
- anxiety (VERY LOW)
- depression (VERY LOW)
- nervousness (VERY LOW)
- amnesia (VERY LOW)
- upper respiratory tract infection (VERY LOW)
- pharyngitis (VERY LOW)
- asthenia (VERY LOW)
- injury (VERY LOW)
- nystagmus (VERY LOW)
- diplopia (VERY LOW)
- diarrhoea (VERY LOW)
- nausea (VERY LOW)
- incidence of memory difficulty (VERY LOW)
- speech difficulty (VERY LOW)
- aggravation of seizures (VERY LOW QUALITY)
- sinusitis (VERY LOW QUALITY)
- coughing (VERY LOW QUALITY)
- mood problems (VERY LOW QUALITY)
- viral infenction (VERY LOW QUALITY)
- otitis media (VERY LOW QUALITY)
- rash (VERY LOW QUALITY)
- purpura (VERY LOW QUALITY)
- fever (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results

Participants in topiramate adjunctive group had significantly worse scores for the following tests compared to placebo group:

- SDMT
- COWA
- Stroop-word
- Stroop-colour

Cost-effectiveness

Available economic evidence indicates that in the treatment of children and adults, topiramate is cost-effective compared to placebo.

- A cost-effectiveness analysis undertaken for the guideline showed that among adults the addition of topiramate was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an expected incremental cost-effectiveness ratio of £15,981 per QALY. This conclusion was consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together in the NCGC base case analysis, adjunctive oxcarbazepine and lamotrigine were likely to represent more cost-effective use of NHS resources. However, in two sensitivity analyses, one where a larger proportion of patients were assumed to achieve seizure freedom from treatment and another when the lowest acquisition cost of all drugs was used, topiramate was likely to be more cost-effective than both oxcarbazepine and lamotrigine (directly applicable and minor limitations).
- One published analysis by Hawkins and colleagues found that topiramate was more costly and more effective at an incremental cost-effectiveness ratio exceeding the NICE willingness to pay threshold; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that among children the addition of topiramate was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £11,022 per QALY. This conclusion is consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, oxcarbazepine dominates adjunctive topiramate and is the most cost effective adjunctive AED given a willingness to pay threshold of £20,000 per QALY gained (directly applicable and minor limitations).
- A published cost-effectiveness by Frew and colleagues found that there was too much uncertainty to reach a definitive conclusion about the relative cost effectiveness of any particular adjunctive AED strategy (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- quality of life outcomes.

10.4.6.9 Topiramate versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Adjunctive sodium valproate was not included in the original economic model as it is not commonly used as adjunctive treatment.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to adverse events. (LOW QUALITY)

No significant difference between topiramate adjunctive therapy and sodium valproate adjunctive therapy for the incidence of:

- memory difficulty (VERY LOW QUALITY)
- speech difficulty (VERY LOW QUALITY)
- depression (VERY LOW QUALITY)

Cognitive outcomes – statistically significant results

Significantly worse scores compared to baseline for immediate recall for topiramate adjunctive therapy and significant improvement compared to baseline for sodium valproate adjunctive therapy.

Cognitive outcomes – statistically non-significant results

No significant change between topiramate adjunctive therapy and sodium valproate adjunctive therapy for scores of cognitive or quality of life on the following measures:

- motor speed/motor fluency
- alertness/reaction speed
- information processing speed
- memory
- profile of Mood States (POMS) scale

Cost-effectiveness

No economic evidence comparing adjunctive topiramate to adjunctive sodium valproate was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- quality of life outcomes.

10.4.6.10 Gabapentin versus Placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of

these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on gabapentin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and placebo for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on gabapentin adjunctive therapy than placebo withdrew due to adverse events. (MODERATE QUALITY)

Significantly more participants on gabapentin adjunctive therapy than placebo experienced the incidence of:

- somnolence (MODERATE QUALITY)
- dizziness (MODERATE QUALITY)
- ataxia (MODERATE QUALITY)
- viral infection, although there is uncertainty over the magnitude of its clinical effect (MODERATE QUALITY)
- fever (MODERATE QUALITY)

Significantly more participants on placebo than gabapentin adjunctive therapy experienced aggravation of seizures. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and placebo for the incidence of:

- nystagmus (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- rhinitis (VERY LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- blurred vision (VERY LOW QUALITY)
- death (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that in the treatment of children and adults, gabapentin is cost-effective compared to placebo.

- A cost-effectiveness analysis undertaken for the guideline showed that among adults the addition of gabapentin was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an expected incremental cost-

effectiveness ratio of £8,034 per QALY. This conclusion was consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together in the NCGC base case analysis, adjunctive oxcarbazepine and lamotrigine were likely to represent more cost-effective use of NHS resources. However, when neither oxcarbazepine nor lamotrigine are suitable gabapentin is likely to be the most cost-effective adjunctive AED (directly applicable and minor limitations).

- One published analysis by Hawkins and colleagues found that for adults gabapenin was more costly and more effective at an incremental cost-effectiveness ratio exceeding the NICE willingness to pay threshold; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that among children the addition of gabapentin was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £3,752 per QALY. This conclusion is consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, oxcarbazepine is the most cost effective adjunctive AED given a willingness to pay threshold of £20,000 per QALY gained (directly applicable and minor limitations).
- A published cost-effectiveness by Frew and colleagues found that there was too much uncertainty to reach a definitive conclusion about the relative cost effectiveness of any particular adjunctive AED strategy (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.4.6.11 Gabapentin versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Adjunctive sodium valproate was not included in the original economic model as it is not commonly used as adjunctive treatment.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and sodium valproate adjunctive therapy for the proportion of participants achieving at least a 50% reduction in seizure frequency (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and sodium valproate adjunctive therapy for the proportion of participants achieving seizure freedom (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and sodium valproate adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive gabapentin to adjunctive sodium valproate was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.4.6.12 Gabapentin versus vigabatrin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of these studies and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and vigabatrin adjunctive therapy for the proportion of participants achieving at least a 50% reduction in seizure frequency (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and vigabatrin adjunctive therapy for the proportion of participants achieving seizure freedom (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and vigabatrin adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

Results of the cost-effectiveness analysis undertaken for the guideline showed adjunctive vigabatrin to be more costly and more effective than adjunctive gabapentin with an incremental cost-effectiveness ratio of £10,712 per QALY (directly applicable and very serious limitations). However, the economic analysis did not take account of the potential long term adverse effects associated with vigabatrin.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.4.6.13 Gabapentin versus lamotrigine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

No significant difference between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the incidence of:

- dizziness (VERY LOW QUALITY)
- diplopia (VERY LOW QUALITY)
- weakness (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- tingling sensation in limbs (VERY LOW QUALITY)
- epigastric discomfort (VERY LOW QUALITY)
- palpilations (VERY LOW QUALITY)
- anxiety (VERY LOW QUALITY)
- phobia (VERY LOW QUALITY)

- amnesia (VERY LOW QUALITY)
- tiredness (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- rashes (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that lamotrigine is cost effective compared to gabapentin.

- One published analysis by Hawkins and colleagues found that adjunctive gabapentin dominated lamotrigine, but their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- Results of the cost-effectiveness analyses undertaken for the guideline also showed that in the treatment of children, young people and adults, adjunctive lamotrigine was more costly and more effective than adjunctive gabapentin.
  - Among adults, the incremental cost-effectiveness ratio for lamotrigine was £4,111. This conclusion was consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, gabapentin is ruled out through extended dominance by lamotrigine and placebo (directly applicable and minor limitations).
  - Among children, the incremental cost-effectiveness ratio for lamotrigine was £17,291. This conclusion is consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.4.6.14 Tiagabine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs, including tiagabine and placebo, used as adjunctive therapy in the treatment of adults with refractory focal seizures was identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on tiagabine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between tiagabine adjunctive therapy and placebo for seizure freedom (VERY LOW QUALITY)

No significant difference between tiagabine adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on tiagabine adjunctive therapy than placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on tiagabine adjunctive therapy than the placebo experienced the incidence of:

- dizziness (LOW QUALITY)
- tremor, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- nervousness, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between tiagabine adjunctive therapy and placebo for incidence of:

- abnormal thinking (VERY LOW QUALITY)
- asthenia (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- infection (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- injury (VERY LOW QUALITY)
- flu syndrome (VERY LOW QUALITY)

Quality of life outcomes – statistically non-significant results

No significant association on the quality of life tests for tiagabine adjunctive therapy and placebo.

Cognitive outcomes – statistically non-significant results

No significant association on the cognitive tests for tiagabine adjunctive therapy and placebo.

Cost-effectiveness

Available economic evidence indicates that adjunctive tiagabine is not cost-effective when compared with placebo.

- One published cost-effectiveness analysis showed adjunctive tiagabine to be more costly and more effective than placebo, but with incremental cost-effectiveness ratios of £25,452 per QALY (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline also showed tiagabine to be more costly and more effective than placebo, but with an ICER of £32,679 per QALY. When all relevant comparators were evaluated together in the NCGC analysis, tiagabine was dominated by adjunctive therapy with levetiracetam, oxcarbazepine, pregabalin and topiramate. Furthermore,

oxcarbazepine and lamotrigine were likely to represent more cost-effective use of NHS resources given the NICE willingness to pay threshold of £20,000 per QALY (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission.

10.4.6.15 Tiagabine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. Tiagabine was included in the model, but phenytoin was not owing to its narrow therapeutic window.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between tiagabine adjunctive therapy and phenytoin adjunctive for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (VERY LOW QUALITY)

Quality of life outcomes – statistically non-significant results

No significant association on the quality of life tests for tiagabine adjunctive therapy and phenytoin adjunctive treatment.

Cognitive outcomes – statistically non-significant results

No significant association on the cognitive tests for tiagabine adjunctive therapy and phenytoin adjunctive treatment.

Cost-effectiveness

No economic evidence comparing adjunctive tiagabine to adjunctive phenytoin was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- time to first seizure
- time to exit/withdrawal of allocated treatment

- time to 12-month remission.

10.4.6.16 Tiagabine versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. Tiagabine was included in the model, but carbamazepine was not as it is most often used as monotherapy.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on carbamazepine adjunctive therapy than tiagabine adjunctive therapy experienced at least 50% reduction in seizure frequency. (MODERATE QUALITY)

Quality of life and cognitive outcomes – statistically significant results

Significant improvement for tiagabine mean scores compared to carbamazepine on the following tests:

- Financial status
- Mood rating scale
- Digit cancellation correct test

Quality of life and cognitive outcomes – statistically non- significant results

No significant difference difference between tiagabine and carbamazepine on mean scores of:

- the QOLIE scale
- WPSI subtests
- Ability tests

Cost-effectiveness

No economic evidence comparing adjunctive tiagabine to adjunctive carbamazepine was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission.

10.4.6.17 Vigabatrin versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Vigabatrin was excluded from one study [181] owing to its potential toxicity. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on vigabatrin adjunctive therapy than placebo experienced at least a 50% reduction in seizure frequency (MODERATE QUALITY)

Significantly more participants on vigabatrin adjunctive therapy than placebo experienced seizure freedom although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between vigabatrin adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on vigabatrin adjunctive therapy than placebo experienced withdrawal due to adverse events (MODERATE QUALITY)

Significantly more participants on vigabatrin adjunctive therapy than the placebo experienced:

- drowsiness (MODERATE QUALITY)
- dizziness (MODERATE QUALITY)

Significantly more participants on placebo than vigabatrin adjunctive therapy experienced aggravation of seizures. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin adjunctive therapy and placebo for the incidence of :

- fatigue (VERY LOW QUALITY)
- nystagmus (VERY LOW QUALITY)
- agitation (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- amnesia (VERY LOW QUALITY)
- abnormal vision (VERY LOW QUALITY)
- weight gain (VERY LOW QUALITY)
- constipation (VERY LOW QUALITY)
- mild depression (VERY LOW QUALITY)

- double vision (VERY LOW QUALITY)
- irritability (VERY LOW QUALITY)
- confusion (VERY LOW QUALITY)
- suicide (VERY LOW QUALITY)
- attempted suicide (VERY LOW QUALITY)

Cognitive events– statistically significant results

Significant improvement for vigabatrin adjunctive therapy mean scores for the following measures compared to placebo:

- motor speed
- flexibility
- design learning task

Significantly worse scores for vigabatrin adjunctive therapy mean scores for the following measures compared to placebo:

- digit cancellation scale
- stroop tests

Cost-effectiveness

Results of the cost-effectiveness analysis undertaken for the guideline showed that adjunctive vigabatrin was more costly and more effective than placebo, with an incremental cost-effectiveness ratio of £9,460 per QALY (directly applicable and very serious limitations). However, the economic analysis did not take account of the potential long term adverse effects associated with vigabatrin which would likely reduce its cost effectiveness relative to other pharmacological options.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- quality of life outcomes.

10.4.6.18 Pregabalin versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on pregabalin adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency (LOW QUALITY)

Significantly more participants on pregabalin adjunctive therapy than placebo experienced seizure freedom (LOW QUALITY)

Significantly more participants on placebo than pregabalin adjunctive therapy experienced withdrawal due to lack of efficacy (MODERATE QUALITY)

Adverse events – statistically significant results

Significantly more participants on pregabalin adjunctive therapy than placebo withdrew due to adverse events. (MODERATE QUALITY)

Significantly more participants on pregabalin adjunctive therapy than the placebo experienced incidence of:

- dizziness (MODERATE QUALITY)
- somnolence (MODERATE QUALITY)
- ataxia (LOW QUALITY)
- weight gain (MODERATE QUALITY)
- vertigo, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- tremor, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- amblyopia (LOW QUALITY)
- diplopia , although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Significantly more participants on placebo than pregabalin adjunctive therapy experienced incidence of headache (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between pregabalin adjunctive therapy and placebo for the incidence of :

- asthenia (LOW QUALITY)
- accidental injury (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that adjunctive pregabalin is not cost effective when compared with placebo.

- Results of the cost-effectiveness analysis undertaken for the guideline showed that the addition of pregabalin was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), but with an expected incremental cost-effectiveness ratio of £22,721 per QALY which exceeds the NICE willingness to pay threshold. Note when all relevant comparators were evaluated together in the NCGC analysis, adjunctive pregabalin was dominated by adjunctive levetiracetam, oxcarbazepine and topiramate. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment

- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.19 Pregabalin versus lamotrigine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of this study and the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statments

Efficacy- statistically significant results

Significantly more participants on pregabalin adjunctive therapy than lamotrigine adjunctive therapy experienced at least 50% reduction in seizure frequency although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between pregabalin adjunctive therapy and lamotrigine adjunctive therapy for seizure freedom. (VERY LOW QUALITY)

No significant difference between pregabalin adjunctive therapy and lamotrigine adjunctive therapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse effects – statistically significant results

Significantly more participants on pregabalin adjunctive therapy than lamotrigine adjunctive therapy experienced incidence of:

- dizziness (LOW QUALITY)
- somnolence, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Significantly more participants on lamotrigine adjunctive therapy than pregabalin adjunctive therapy experienced incidence of headache (LOW QUALITY).

Adverse effects – statistically non-significant results

No significant difference between pregabalin adjunctive therapy and lamotrigine adjunctive therapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between pregabalin adjunctive therapy and lamotrigine adjunctive therapy for incidence of:

- asthenia (VERY LOW QUALITY)
- infection (VERY LOW QUALITY)

- diplopia (VERY LOW QUALITY)
- vertigo (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that adjunctive pregabalin is not cost-effective when compared with adjunctive lamotrigine.

- Results of the cost-effectiveness analysis undertaken for the guideline showed that the addition of pregablin was associated with both increased costs and better health outcomes (higher QALYs) than the addition of lamotrigine, but with an unacceptably high incremental cost-effectiveness ratio of £50,270 per QALY which exceeds the NICE willingness to pay threshold. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.4.6.20 Clobazam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Clobazam was not included in the original economic model owing to its sedative side effects and the fact that their effectiveness may wane with long term and continuous use.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on clobazam adjunctive therapy than placebo experienced seizure freedom, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between clobazam adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse effects – statistically non significant results

No significant difference between clobazam adjunctive therapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive clobazam to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.4.6.21 Lacosamide versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on lacosamide adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between lacosamide adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)

No significant difference between lacosamide adjunctive therapy and placebo for withdrawal due to lack of efficacy (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on lacosamide adjunctive therapy than placebo withdrew due to adverse events (LOW QUALITY)

Significantly more participants on lacosamide adjunctive therapy than the placebo experienced:

- dizziness (LOW QUALITY)
- vomiting, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- diplopia, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- vision blurred, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lacosamide adjunctive therapy and placebo for the incidence of :

- headache (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- URI (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that adjunctive lacosamide is not cost effective when compared with placebo.

- Results of the cost-effectiveness analysis undertaken for the guideline showed that the addition of lacosamide was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), but with an expected incremental cost-effectiveness ratio of £66,256 per QALY which exceeds the NICE willingness to pay threshold. Note when all relevant comparators were evaluated together in the NCGC analysis, adjunctive lacosamide was the least effective and third most costly adjunctive AED. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.22 Zonisamide versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on zonisamide adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between zonisamide adjunctive therapy and placebo for seizure freedom. (VERY LOW QUALITY)

No significant difference between zonisamide adjunctive therapy and placebo for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on zonisamide adjunctive therapy than placebo withdrew due to adverse events (MODERATE QUALITY)

Significantly more participants on zonisamide adjunctive therapy than the placebo experienced in the titration period:

- dizziness, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- somnolence (titration phase) although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Significantly more participants on placebo than zonisamide adjunctive therapy experienced aggravation of seizures. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between zonisamide adjunctive therapy and placebo for incidence of:

- somnolence (fixed dose phase) (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- abnormal thinking (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)
- rhinitis (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- nausea or vomiting (VERY LOW QUALITY)
- death (VERY LOW QUALITY)
- increase in liver enzymes
- decreased leukocyte count
- decreased platelet count
- increase in serum creatinine
- weight gain
- weight loss

Cost-effectiveness

Available economic evidence indicates that adjunctive zonisamide is not cost effective when compared with placebo.

- Results of the cost-effectiveness analysis undertaken for the guideline showed that the addition of zonisamide was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), but with an expected incremental cost-effectiveness ratio of £68,397 per QALY which exceeds the NICE willingness to pay threshold. Note when all relevant comparators were evaluated together in the NCGC analysis, adjunctive lacosamide was the third least effective and second most costly adjunctive AED. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.23 Eslicarbazepine acetate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adults with refractory focal seizures. The complete results of the NCGC adults adjunctive therapy model are presented in section 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on eslicarbazepine acetate adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (LOW QUALITY)

Significantly more participants on eslicarbazepine acetate adjunctive therapy than placebo experienced seizure freedom. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between eslicarbazepine acetate adjunctive therapy and placebo for withdrawal due to lack of efficacy (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on eslicarbazepine acetate adjunctive therapy than placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on eslicarbazepine acetate adjunctive therapy than placebo had an incidence of:

- dizziness (LOW QUALITY)
- nausea (LOW QUALITY)
- diplopia, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Adverse events – statistically non- significant results

No significant difference between eslicarbazepine acetate adjunctive therapy and placebo for the incidence of:

- aggravation of seizures (VERY LOW QUALITY)
- death (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)

- headache (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that adjunctive eslicarbazepine acetate is not cost effective when compared with placebo.

- Results of the cost-effectiveness analysis undertaken for the guideline showed that the addition of eslicarbazepine acetate was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), but with an expected incremental cost-effectiveness ratio of £53,585 per QALY which exceeds the NICE willingness to pay threshold. Note when all relevant comparators were evaluated together in the NCGC analysis, adjunctive eslicarbazepine acetate was dominated by adjunctive levetiracetam, oxcarbazepine, pregabalin and topiramate. This conclusion was consistent across a range of sensitivity analyses (directly applicable and minor limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.24 Felbamate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Felbamate was not included among comparators in the NCGC economic model for adjunctive AED treatment for refractory focal seizures due to its potential for serious adverse effects and its limited use on a 'named patient' basis.

Evidence statements

Adverse events – statistically significant results

Significantly more participants on felbamate adjunctive therapy than the placebo experienced:

- headache (MODERATE QUALITY)
- insomnia, although there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)
- nausea, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between felbamate adjunctive therapy and placebo for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between felbamate adjunctive therapy and placebo for the incidence of:

- dyspepsia (VERY LOW QUALITY)

- dizziness (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- constipation (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- anxiety (VERY LOW QUALITY)
- vomiting (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive felbabamate to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.25 Oxcarbazepine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] of AEDs used as adjunctive therapy in the treatment of adults and one economic evaluation[184] of AEDs used in the treatment of children and young people with refractory focal seizures were identified in the economic literature search. As there were still gaps in the economic evidence base, two original economic models were developed to compare AEDs used as adjunctive therapy in the treatment of refractory focal seizures: one model for the evaluation of treatment for adults and another specifically for children and young people. The complete results of these published studies and the NCGC adjunctive therapy models are presented in sections 10.4.7 and 10.4.8.

Evidence statements

Efficacy- statistically significant results

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced seizure freedom, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine adjunctive therapy and placebo for the withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on oxcarbazepine adjunctive therapy than the placebo withdrew due to adverse events. (LOW QUALITY)

Significantly more participants on oxcarbazepine adjunctive therapy than placebo experienced an incidence of:

- headache (VERY LOW QUALITY)
- dizziness (LOW QUALITY)
- somnolence (LOW QUALITY)
- ataxia (LOW QUALITY)
- nystagmus (LOW QUALITY)
- abnormal gait, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- vomiting (VERY LOW QUALITY)
- vertigo, although there is uncertainty over the magnitude of its clinical effect (LOW QUALITY)
- nausea (LOW QUALITY)
- diplopia, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)
- abnormal vision (LOW QUALITY)
- fatigue (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between oxcarbazepine adjunctive therapy and placebo for the incidence of:

- abdominal pain (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- fever (VERY LOW QUALITY)
- rhinitis (VERY LOW QUALITY)
- pharyngitis (VERY LOW QUALITY)
- upper respiratory infection (VERY LOW QUALITY)
- viral infection (VERY LOW QUALITY)

Cost-effectiveness

Available economic evidence indicates that in the treatment of children, young people and adults, adjunctive oxcarbazepine is cost effective when compared with placebo.

- A cost-effectiveness analysis undertaken for the guideline showed that among adults, the addition of oxcarbazepine was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £13,983 per QALY. This conclusion is consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, oxcarbazepine is the most cost effective adjunctive AED if the willingness to pay threshold is at least £23,000 per QALY or when lamotrigine is not a relevant treatment option (directly applicable and minor limitations).

- One published analysis by Hawkins and colleagues found that for adults oxcarbazepine was more costly and more effective at an incremental cost-effectiveness ratio of £17,095; however, their analysis was based on a now out-of-date systematic review and 2002-03 costs (partially applicable and potentially serious limitations).
- A cost-effectiveness analysis undertaken for the guideline showed that among children, the addition of oxcarbazepine was associated with increased costs and better health outcomes (higher QALYs) than continuation of existing therapy alone (placebo), with an incremental cost-effectiveness ratio of £8,436 per QALY. This conclusion is consistent across a range of sensitivity analyses. Note that when all relevant comparators were evaluated together, oxcarbazepine is the most cost effective adjunctive AED given a willingness to pay threshold of £20,000 per QALY gained (directly applicable and minor limitations).
- A published cost-effectiveness by Frew and colleagues found that there was too much uncertainty to reach a definitive conclusion about the relative cost effectiveness of any particular adjunctive AED strategy (partially applicable and potentially serious limitations).

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.4.6.26 Sodium valproate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Sodium valproate was not included among comparators in the NCGC economic model for adjunctive treatment for refractory focal seizures because it is most commonly used as a first line monotherapy.

Evidence statements

Adverse events - statistically non significant results

No significant difference between sodium valproate adjunctive therapy and placebo for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive sodium valproate to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- 50% reduction in seizure frequency
- withdrawal due to lack of efficacy

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.4.6.27 Primidone versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. Neither sodium valproate nor primidone were included in the NCGC economic model of adjunctive AEDs used in the treatment of refractory focal seizures as sodium valproate is most commonly used as first line.

Evidence statements

Efficacy - statistically significant results

Significantly more participants on sodium valproate than primidone had at least 50% reduction in seizure frequency, although there is uncertainty over the magnitude of its clinical effect. (VERY LOW QUALITY)

Efficacy - statistically non-significant results

No significant difference between primidone and sodium valproate for seizure freedom. (VERY LOW QUALITY)

Adverse events - statistically non-significant results

No significant difference between primidone and sodium valproate for withdrawal due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive sodium valproate to adjunctive primidone was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.4.7 Health economic evidence of AEDs used as adjunctive therapy for adults with refractory focal epilepsy

11 studies published since the systematic review [40,276] of economic studies undertaken to inform TA76 and TA79 were identified in the economic literature search. Nine of these studies[277-285] were excluded from the economic evidence review due to poor applicability or very serious limitations. Full details of exclusion are included in appendix M.

Two studies [181,286] assessing the cost-effectiveness of AEDs used as adjunctive therapy in adults with refractory focal epilepsy were included in the economic evidence review. See economic evidence tables in appendix M for study details, including quality assessments of their methodology and applicability. As there were still gaps in the economic evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in adult patients with refractory focal epilepsy. This was based on clinical evidence from pairwise meta-analyses of placebo controlled-trials (see section 10.4.6). See appendix Q for full details and results of modelling.

Economic study characteristics

Table 11: Adjunctive therapy for adults with refractory focal epilepsy - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCGC Model – adults adjunctive therapy (see Appendix Q for details)	Minor limitations	Directly applicable	Decision analytic model; comparators included placebo, lamotrigine, oxcarbazepine, gabapentin, topiramate, levetiracetam, tiagabine, pregabalin, lacosamide, eslicarbazepine acetate, zonisamide and vigabatrin; time horizon 15 years; clinical data based on pair-wise meta-analyses of placebo controlled trials
Hawkins (2005)[181]	Potentially serious limitations (a)	Partially applicable (b, c)	Decision analytic model; comparators included placebo, lamotrigine, gabapentin, tiagabine, oxcarbazepine, topiramate, levetiracetam; time horizon 15 years; clinical data based on network meta-analysis that included some studies with mixed focal and generalised epilepsy populations
Spackman (2007)[286]	Potentially serious limitations	Partially applicable (b)	Decision analytic model; comparators included zonisamide and levetiracetam; time horizon 15 years

(a) Unit costs of interventions are from 2002/03 and since publication, lamotrigine has come off patent and the non-proprietary price is dramatically lower
(b) Study did not include all comparators considered relevant to the GDG, namely the newer AEDs.
(c) Costs and effects discounted at 6% and 1.5% per annum, respectively.

Economic study results

NCGC adults adjunctive therapy model (directly applicable, minor limitations)

For full details of base case and all sensitivity analyses, see appendix Q.

Table 12: Adjunctive therapy for adults with refractory focal seizures – Summary of NCGC model findings

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
Placebo	£8,928	8.197		At £20K per QALY threshold, probability most cost-effective Base case: 4% Alternative seizure free values: 1% All cheapest: 0% Excluding LTG and OXC: 13% LEV cost 30% and 50% reduced: 3% and 2% At £30K per QALY threshold: 1%
GBP	£9,394	8.255	£8,035 (ext dom)	At £20K per QALY threshold, probability most cost-effective Base case: 23% Alternative seizure free values: 26% All cheapest: 18% Excluding LTG and OXC: 43% LEV cost 30% and 50% reduced: 21% and 16% At £30K per QALY threshold: 16%
LTG	£9,431	8.264	£7,507	At £20K per QALY threshold, probability most cost-effective Base case: 31% Alternative seizure free values: 25% All cheapest: 29% LEV cost 30% and 50% reduced: 27% and 22% At £30K per QALY threshold: 24%
OXC	£10,564	8.314	£22,660	At £20K per QALY threshold, probability most cost-effective Base case: 22% Alternative seizure free values: 11% All cheapest: 17% LEV cost 30% and 50% reduced: 18% and 15% At £30K per QALY threshold: 27%
TPM	£10,606	8.302	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 11% Alternative seizure free values: 28% All cheapest: 32% Excluding LTG and OXC: 24% LEV cost 30% and 50% reduced: 9%

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
				and 7% At £30K per QALY threshold: 15%
LEV	£11,157	8.316	£296,500	At £20K per QALY threshold, probability most cost-effective Base case: 6% Alternative seizure free values: 2% All cheapest: 2% Excluding LTG and OXC: 13% LEV cost 30% and 50% reduced: 19% and 36% At £30K per QALY threshold: 10%
PGB	£11,291	8.301	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 2% Alternative seizure free values: 4% All cheapest: 1% Excluding LTG and OXC: 6% LEV cost 30% and 50% reduced: 2% and 1% At £30K per QALY threshold: 4%
TGB	£11,673	8.281	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 1% Alternative seizure free values: 3% All cheapest: 0% Excluding LTG and OXC: 2% LEV cost 30% and 50% reduced: 1% and 1% At £30K per QALY threshold: 2%
LAC	£11,777	8.24	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% Alternative seizure free values: 0% All cheapest: 0% Excluding LTG and OXC: 0% LEV cost 30% and 50% reduced: 0% and 0% At £30K per QALY threshold: 0%
ZON	£13,237	8.26	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% Alternative seizure free values: 0% All cheapest: 0% Excluding LTG and OXC: 0% LEV cost 30% and 50% reduced: 0% and 0% At £30K per QALY threshold: 0%
ESL	£13,322	8.279	Dominate	At £20K per QALY threshold,

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
			d	probability most cost-effective Base case: 0% Alternative seizure free values: 0% All cheapest: 0% Excluding LTG and OXC: 0% LEV cost 30% and 50% reduced: 0% and 0% At £30K per QALY threshold: 0%

Note: VGB was included in an analysis, and was found to be very cost-effective (£11,754compared tolamotrigine). This finding is not presented here as the model does not adequately capture the potential harms of vision defect that have been associated with long term use of VGB.

Evidence statements

Results of the base case found that lamotrigine was likely to be the most cost-effective AED for the adjunctive treatment of adults with refractory focal seizures. Oxcarbazepine may also be cost-effective as adjunctive therapy in this population. There is considerable uncertainty in these results.

In circumstances where lamotrigine and oxcarbazepine have been previously tried and found to be ineffective or not tolerated, gabapentin or topiramate are likely to be cost-effective adjunctive AEDs.

Results of the analysis showed that levetiracetam is the most effective adjunctive therapy, but that at June 2011 costs, its additional cost compared to lamotrigine and oxcarbazepine is not justified by the additional benefit. However, with only a 30 percent reduction in its unit cost, levetiracetam is likely to dominate oxcarbazepine and be considered cost-effective compared to lamotrigine.

Adjunctive treatment with oxcarbazepine or levetiracetam dominates adjunctive treatment with newer AEDs including eslicarbazepine acetate, lacosamide, pregabalin, tiagabine and zonisamide.

Hawkins 2005[181] (partially applicable, potentially serious limitations)

See economic evidence table in appendix M for study details.

Table 13: Adjunctive therapy for adults with refractory focal epilepsy – Summary of Hawkins 2005[181] findings

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
Placebo	£5,064	8.716		At £20K per QALY threshold, probability most cost-effective Base case: 40% Excluding LTG and OXC: 58%
GBP	£5,861	8.747	Extended Dominance	At £20K per QALY threshold, probability most cost-effective Base case: 2% Excluding LTG and OXC: 12%
LTG	£5,926	8.746	Extended Dominance	At £20K per QALY threshold, probability most cost-effective Base case: 2%
TGB	£6,133	8.758	Extended Dominance	At £20K per QALY threshold, probability most cost-effective Base case: 2% Excluding LTG and OXC: 16%

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
OXC	£6,400	8.794	£17,095	At £20K per QALY threshold, probability most cost-effective Base case: 52%
LEV	£6,984	8.775	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 2% Excluding LTG and OXC: 7%
TPM	£7,026	8.777	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 0% Excluding LTG and OXC: 5%

Evidence statements

Adjunctive oxcarbazepine is the most effective and most cost-effective AED among evaluated adjunctive AEDs (partially applicable and potentially serious limitations).

Adjunctive gabapentin, adjunctive lamotrigine and adjunctive tiagabine are ruled out through extended dominance by adjunctive oxcarbazepine and placebo (monotherapy) (partially applicable and potentially serious limitations).

Adjunctive levetiracetam and adjunctive topiramate are more costly and less effective than adjunctive oxcarbazepine (partially applicable and potentially serious limitations).

Spackman 2007[286] (directly applicable, potentially serious limitations)

See economic evidence table in appendix M for details.

Table 14: Adjunctive therapy for adults with refractory focal epilepsy – Summary of Spackman 2007 [286]findings

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
LEV	£15,610	7.897		
ZON	£15,630	7.923	£761	No probabilistic sensitivity analysis was performed. The results did not change dramatically in one-way sensitivity analyses of discounting rates, shorter time horizon, variation to proportion of responders, variation in utility weights. Annual cost of each AED did impact results: cost of LEV halved or cost of ZON doubled makes ICER of ZON £45K+.

Evidence statements

Adjunctive zonisamide is cost-effective compared to adjunctive levetiracetam (partially applicable and potentially serious limitations). However, other economic evaluations showed both levetiracetam and zonisamide to be more costly and less effective than other adjunctive AEDs.

10.4.8 Health economic evidence of AEDs used as adjunctive therapy for children with refractory focal epilepsy

One study[184] assessing the cost-effectiveness of AEDs used as adjunctive therapy in children with refractory focal epilepsy was identified in the economic literature search and included in the economic evidence review. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in children with refractory focal epilepsy. This was based on clinical evidence from pairwise meta-analyses of placebo controlled-trials (see section 10.4.6). See appendix R for full details and results of modelling.

Economic study characteristics

Table 15: Adjunctive therapy for children with refractory focal epilepsy - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCGC Model – children adjunctive therapy (see Appendix R for details)	Minor limitations	Directly applicable	Decision analytic model; comparators included placebo, gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate; time horizon 15 years; clinical data based on pairwise meta-analyses of placebo controlled trials.
Frew (2007) [184]	Potentially serious limitations (a)	Partially applicable (b, c)	Decision analytic model; comparators were treatment sequences including gabapentin, lamotrigine, oxcarbazepine and topiramate as possible adjunctive therapy all compared to a baseline of only older AEDs (carbamazepine, sodium valproate and phenytoin); time horizon up to 15 years; clinical data based on Nieto-Barrera 2001 [164], Zamponi 1999 [183];

(a) 2002/03 UK pounds
(b) Costs discounted at 6% per annum; Effects discounted at 1.5% per annum
(c) Analysis did not include all comparators of interest to the GDG, namely levetiracetam.

Economic study results

NCGC Model – children adjunctive therapy (directly applicable, minor limitations)

For full details of base case and all sensitivity analyses, see appendix R.

Table 16: Adjunctive therapy for children with refractory focal epilepsy – Results from NCGC 2010

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
Placebo	£18,819	9.409		At £20K per QALY threshold, probability most cost-effective Base case: 35% Alternative seizure free values: 9% All cheapest: 1% LEV cost 30% and 50% reduced: 35% and 34% Excluding LTG and OXC: 42% Cohort starting age=10 yrs: 42% At £30K per QALY threshold: 24%
GBP	£19,018	9.462	£3,752	At £20K per QALY threshold, probability most cost-effective Base case: 18% Alternative seizure free values: 40% All cheapest: 20% LEV cost 30% and 50% reduced: 17% and 15% Excluding LTG and OXC: 31% Cohort starting age=10 yrs: 16% At £30K per QALY threshold: 19%
LTG	£19,174	9.471	£17,291 (ext dom)	At £20K per QALY threshold, probability most cost-effective Base case: 15% Alternative seizure free values: 17% All cheapest: 41% LEV cost 30% and 50% reduced: 14% and 12% Cohort starting age=10 yrs: 15% At £30K per QALY threshold: 17%
OXC	£19,764	9.521	£12,644	At £20K per QALY threshold, probability most cost-effective Base case: 19% Alternative seizure free values: 7% All cheapest: 17% LEV cost 30% and 50% reduced: 18% and 14% Cohort starting age=10 yrs: 17% At £30K per QALY threshold: 24%
TPM	£19,922	9.509	Dominated	At £20K per QALY threshold, probability most cost-effective Base case: 7% Alternative seizure free values: 24% All cheapest: 17% LEV cost 30% and 50% reduced: 5% and 5% Excluding LTG and OXC: 14% Cohort starting age=10 yrs: 6% At £30K per QALY threshold: 8%

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
LEV	£20,448	9.523	£341,875	At £20K per QALY threshold, probability most cost-effective Base case: 6% Alternative seizure free values: 3% All cheapest: 4% LEV cost 30% and 50% reduced: 11% and 20% Excluding LTG and OXC: 14% Cohort starting age=10 yrs: 4% At £30K per QALY threshold: 8%

Evidence statements

There was considerable uncertainty in the results of the economic evaluation of different AEDs used in the treatment of children who have failed first-line AEDs. No single AED could be identified as clearly cost-effective, although based on the expected costs and QALYs, oxcarbazepine is likely to be cost-effective. Sensitivity analyses around unit costs also indicated that lamotrigine may be cost-effective if costs are reduced compared to the base case.

In circumstances where lamotrigine and oxcarbazepine have been previously tried and found to be ineffective or not tolerated, gabapentin or topiramate are likely to be cost-effective adjunctive AEDs.

Results of the analysis showed that levetiracetam is the most effective adjunctive therapy, but that at current costs, its additional cost compared to alternative AEDs is not justified by the additional benefit; however this conclusion is very sensitive to changes in its unit cost. Given a 50 percent reduction it is likely to dominate oxcarbazepine and be considered cost-effective compared to lamotrigine. Given a 30 percent reduction in its unit cost, levetiracetam is likely to be optimal when oxcarbazepine and lamotrigine are inappropriate.

Frew 2007 [184](partially applicable, potentially serious limitations)

See economic evidence table in appendix M for details.

Table 17: Adjunctive therapy for children with refractory focal epilepsy – Results from Frew 2007[184]

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
Baseline (no new AEDs)	Point estimates cannot be determined from the data provided			At £20K per QALY threshold, probability most cost-effective Base case: 0%
TPM (adjunctive therapy)	Point estimates cannot be determined from the data provided		More costly and possibly more effective, but ICER cannot be determined from the data provided.	At £20K per QALY threshold, probability most cost-effective Base case: 30%
OXC (adjunctive therapy)	Point estimates cannot be determined from the data provided		Likely dominated	At £20K per QALY threshold, probability most cost-effective Base case: 30%
LTG (second line monotherapy)	Point estimates cannot be determined from		Likely dominated	At £20K per QALY threshold, probability most cost-effective

AED	Total cost (£) per patient	Total effects (QALYs)	ICER (£ / QALY)	Uncertainty
	the data provided			Base case: 23%
LTG (adjunctive therapy)	Point estimates cannot be determined from the data provided		Likely dominated	At £20K per QALY threshold, probability most cost-effective Base case: 23%
GBP (adjunctive therapy)	Point estimates cannot be determined from the data provided		Likely dominated	At £20K per QALY threshold, probability most cost-effective Base case: 18%

Evidence statements

Cost-effectiveness of adjunctive AEDs including gabapentin, lamotrigine, oxcarbazepine and topiramate compared to a baseline strategy of only older AEDs is highly uncertain. No definitive conclusion about relative cost-effectiveness can be determined.

10.4.9 New recommendations and link to evidence

Adjunctive treatment in children, young people and adults with refractory focal seizures

NICE has also issued guidance on the use of retigabine as an option for the adjunctive treatment of partial (focal has been used in this guideline) onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy in 'Retigabine for the adjunctive treatment of partial onset seizures in epilepsy' (NICE technology appraisal guidance 232).

Recommendation	**88. Offer carbamazepine, clobazam*, gabapentin*, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments (see recommendations 85 and 86) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	In children, young people and adults, the achievement of seizure freedom or at least a 50% reduction in seizure frequency were considered to be the most clinically relevant outcomes. Tolerability, as measured by withdrawals due to adverse events, was also considered important.
Trade off between clinical benefits and harms	The evidence for adults showed that significantly more participants receiving clobazam, levetiracetam, levetiracetam extended-release, oxcarbazepine and topiramate achieved seizure freedom than placebo. Significantly more on gabapentin, oxcarbazepine, lamotrigine, levetiracetam and topiramate experienced at least a 50% reduction in seizure frequency when compared to placebo. From the evidence for children, significantly more participants on lamotrigine and oxcarbazepine compared to placebo experienced at least a 50% reduction in seizure frequency. More people on oxcarbazepine (adults and children) achieved seizure freedom than those on placebo in a refractory population on monotherapy. In children, significantly more participants on levetiracetam compared to placebo experienced at least a 50% reduction in seizure frequency. The drugs recommended above had unfavourable adverse events profiles, but the GDG found this unsurprising given that they were being evaluated as combination treatment in a refractory population. Many of the adverse events observed in the trials were dose related and in clinical practice these can be mitigated through careful dose titration. Significantly more participants receiving gabapentin, lamotrigine, topiramate and oxcarbazepine withdrew due to adverse events compared to placebo. Gabapentin had higher incidence of somnolence, dizziness and ataxia and aggravation of seizures when compared to placebo. There was no significant difference between levetiracetam and placebo for withdrawal due to adverse events although incidence of adverse events was significantly higher in the levetiracetam arm. No specific adverse events were reported in the trial for clobazam, but the GDG considered its tendency to have sedative side effects and its efficacy can wane over extended use. Oxcarbazepine and lamotrigine had a less favourable adverse events profile compared to placebo. Topiramate had higher incidence of headache when compared with lamotrigine. In children taking lamotrigine the incidence of dizziness, tremor, nausea and ataxia were higher

* At the time of publication (Janaury 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	compared to to placebo. A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. For the drugs recommended here, the treatment benefits outweighed the harms for the average patient and the QALYs gained justified the additional costs over placebo (no adjunctive AED).
Economic considerations	Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. The original cost-effectiveness analysis undertaken for the guideline indicates that there is considerable uncertainty as to which AED represents the optimal use of NHS resources as a great deal depends on what is appropriate for the individual patient and on his/her previous treatment history. The GDG chose to recommend lamotrigine and oxcarbazepine on the basis that they were the two AEDs with the greatest probability of being cost-effective in the base case and other scenarios. Therefore, if either lamotrigine or oxcarbazepine have not been tried as monotherapy, either first or second-line, then they are likely to represent cost-effective choice s to add-in as adjunctive therapy. The GDG felt that some combinations might be more effective or more tolerable, and thus might be more cost effective, but neither the clinical evidence review nor economic model was designed to identify particular AED combinations. Given that lamotrigine and oxcarbazepine are among AEDs recommended as first-line treatment of newly diagnosed focal seizures, a patient with refractory focal seizures requiring further treatment may have already tried one or both. The GDG recommended gabapentin on the basis that in the base case, it was likely to be the most cost-effective AED when lamotrigine and oxcarbazepine were not relevant treatment options. However, given the uncertainty highlighted by the results of the other sensitivity analyses, particularly around the estimates of seizure freedom and assumptions of cost, the GDG decided to recommend topiramate as an additional choice for adjunctive therapy. The GDG considered the results of the base case analysis, in which levetiracetam, although the most effective adjunctive AED, was not shown to be cost-effective given the NICE willingness to pay threshold. It was also unlikely to be considered cost-effective compared to gabapentin and topiramate when lamotrigine and oxcarbazepine were removed from the analysis (assuming they have been already tried as monotherapy). The GDG looked to a series of sensitivity analyses around projected reductions in the price of levetiracetam in order to determine the price point at

	which the drug might become cost effective. The sensitivity analyses showed that the unit cost of levetiracetam need only come down by 30 percent in order to dominate oxcarbazepine and be considered cost-effective compared to lamotrigine (ICER=£19,264 per QALY). It also becomes the most cost-effective drug under the £20,000 per QALY threshold when lamotrigine and oxcarbazepine are excluded; that is, levetiracetam dominates topiramate (even when only non-proprietary costs are used) and has an ICER of £17,213 compared to gabapentin. The GDG considered the uncertainties around levetiracetam and how its future cost might impact its relative cost effectiveness compared to other available AEDs used in the treatment of refractory focal seizures. They also accepted that they knew neither how much the price of levetiracetam will drop with the introduction of generic competition, nor how much the cost of other AEDs might change as well. The GDG considered the dramatic reduction in the cost of other AEDs, such as lamotrigine and topiramate, following loss of patent protection and introduction of generic competition. Looking to these other examples, they considered it very likely that a similar reduction would occur for levetiracetam soon after publication of the guideline and that a recommendation without levetiracetam would quickly become inaccurate. They also considered the widespread use of levetiracetam in current clinical practice, based not only on their own experience but also on the feedback of stakeholders during consultation of the guideline. Considering the evidence, the uncertainties and their clinical experience, the GDG therefore determined that levetiracetam should be offered among initial adjunctive therapy options.
Quality of evidence	For adults, the majority of the evidence was placebo controlled and there were few head to head comparisons. All of the studies were randomised controlled trials, the majority of which were double-blind. Most of the studies gave unclear details of their methods of randomisation, allocation concealment and blinding. The statistically significant results for 50% reduction in seizure frequency were from the placebo-controlled studies. Few of the drugs which were compared to drugswere statistically significant and where this did occur there was uncertainty in the magnitude of clinical effect. The quality overall was generally low or very low. The published economic evidence varied had problems of methodological quality and applicability to the decision-making context of the guideline. Some had out of date costs that could change the study's conclusions or did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.

Other considerations	The drugs recommended above are older and therefore there is long-term experience with them. Eslicarbazepine acetate, lacosamide, pregabalin, and zonisamide showed efficacy but were not included for first-line adjunctive treatment as they are newer drugs and the GDG felt that there needed to be more long-term evidence of their efficacy and cost-effectiveness for adjunctive treatment. There is limited evidence for tiagabine being effective. Gabapentin was included as first-line adjunctive drug option, but based on the clinical experience of the GDG was regarded as less effective than the other AEDs. The GDG considered the addition of oxcarbazepine without trying carbamazepine as unusual but may be considered, as it is less enzyme inducing. The GDG were aware that in clinical practice a second AED is added to the first. They also agreed with published literature which states that if the latter helps the first may be taken away if the patient agrees.[287] GDG discussion centred around some key issues. Namely, care should be taken with clobazam when withdrawing and a slow withdrawal of clobazam over/up to 4-6mg in view of the risk of withdrawal seizures. They noted that sodium valproate inhibits the metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. Clinical experience led the GDG to believe that on withdrawal of sodium valproate, lamotrigine levels may drop and this may be ther reason for breakthrough seizures. They also noted that there should be a concomitant increase in the lamotrigine dose but did not wish to make a specific recommendation. Topiramate may affect phenytoin levels. NICE has also issued guidance on the use of retigabine as an option for the adjunctive treatment of partial (focal has been used in this guideline) onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy in 'Retigabine for the adjunctive treatment of partial onset seizures in epilepsy' (NICE technology appraisal guidance 232).

Recommendation	**89. If adjunctive treatment (see recommendation 88) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin*, tiagabine, vigabatrin and zonisamide*. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [new 2012]**
Relative values of different outcomes	In adults and children, achievement of at least a 50% reduction in seizure frequency was an important outcome. These AEDs have evidence of efficacy in some patients, and may benefit patients who have not responded to and /or who have experienced adverse effects with other AEDs.
Trade off between clinical benefits and harms	The balance of benefit and adverse effects needs to be carefully monitored in all patients, and it must be recognised that different individuals may have different responses to various AEDs. From the direct evidence for adults, lacosamide, zonisamide, eslicarbazepine acetate, tiagabine, vigabatrin and pregabalin had more participants with at least 50% reduction in seizure frequency when compared to placebo. Eslicarbazepine acetate, and pregabalin also had more seizure freedom than placebo. Phenobarbital was added by the GDG based on their professional opinion. Tiagabine was found to have no difference when compared to lamotrigine, levetiracetam or phenytoin. In terms of efficacy, there was no significant difference between vigabatrin and gabapentin. Also pregabalin was shown to have a less favourable adverse events profile, causing greater withdrawal due to adverse events than placebo. Eslicarbazepine acetate, lacosamide, vigabatrin, zonisamide and tiagabine had more withdrawal due to adverse events and more adverse events than than placebo arm. There was no difference between phenytoin and tiagabine or lamotrigine and tiagabine for withdrawal due to adverse events. Vigabatrin has a harmful and irreversible side effects profile with retinal toxicity causing visual impairment, according to the GDG expertise and epilepsy literature. These side effects occur over the longer term and would not be observed in any of the short term trials combined in the evidence. The GDG were aware that primidone had previously been recommended for adjunctive therapy for focal seizures in the 2004 guideline. However, because of the results of the evidence review that clearly demonstrated the improved clinical and cost effectiveness of other AEDs, the GDG did not wish to make a recommendation for the use of primidone. The GDG's clinical

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	opinion was that primidone is now rarely used in initiating antiepileptic therapy and is only offered to individuals as a continuing prescription. It is not used in children as a first line therapy. A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. The drugs recommended for consideration here were effective to varying degress, but the treatment benefits, in terms of QALYs gained, or in some cases lost, did not justified the additional costs over drugs recommended in the previous recommendation (gabapentin, lamotrigine, oxcarbazepine, topiramate).
Economic considerations	Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. One published study showed adjunctive zonisamide to be cost-effective compared to adjunctive levetiracetam, but in all other studies and/or in the original modelling work undertaken for the guideline, neither levetiracetam nor zonisamide were shown to be cost-effective compared to alternative AEDs. In the economic analysis undertaken for the guideline, eslicarbazepine acetate, lacosamide, pregabalin, tiagabine and zonisamide were all more costly and less effective than other cost-effective treatment alternatives. Therefore, the GDG felt that they should not be recommended among initial adjunctive therapy options. Rather these drugs should be considered only for cases where previously recommended drugs are contraindicated or have been tried and were either ineffective or not tolerated. Vigabatrin was specifically excluded from various published economic evaluations due to its potential for long term toxicity and adverse effects. It was included in the original economic analysis undertaken for this guideline and was shown to be very effective and cost-effective. However, a very serious limitation of the model was that it did not account for vigabatrin's potential for long term toxicity and development of visual field defects. Vigabatrin's cost-effectiveness in the model was driven by its efficacy and relatively low rates of withdrawal due to adverse events from short term trial data. Had the model accounted for long term, irreversible effects to vision, it is unlikely to have performed quite as well. The GDG recognised its relative effectiveness over other AEDs, and considered the risk of long term visual field defect to outweigh its clinical benefit. The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome.
Quality of evidence	Overall the quality of evidence was low and most of the studies

	had unclear or no details of randomisation, allocation concealment or blinding and higher drop-out in the treatment arms. There was no evidence found for phenobarbital but this recommendation is based on GDG expertise. The published economic evidence had problems of methodological quality and applicability to the decision-making context of the guideline. Some had out of date costs that could change the study's conclusions or did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Due to this limitation, results concerning vigabatrin's cost-effectiveness were of limited value to GDG decision-making. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.
Other considerations	The GDG consensus opinion was that management should be discussed with patients or they should be offered referral to, a tertiary epilepsy specialist if adjunctive treatment with AEDs listed in recommendation 1.13.2.1 is ineffective or not tolerated because achieving successful treatment may be complex. They noted that long term experience with some of these drugs (pregabalin, lacosamide, zonisamide and eslicarbazepine acetate) is limited. The GDG discussed the fact that care should be taken when withdrawing phenobarbital and should be slowly withdrawn in view of the risk of withdrawal seizures but did not wish to make a specific recommendation in this area. The group discussed the need for careful evaluation of risk/benefit for each individual to be undertaken for each individual and the final GDG consensus opinion was that vigabatrin should only be prescribed in tertiary epilepsy specialist care.

10.4.10 Research Recommendations (for full list see section 2.11)

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

a. Focal seizures: carbamazepine, eslicarbazepine acetate, lamotrigine, lacosamide, levetiracetam, pregabalin and zonisamide.

b. Generalised seizures: lamotrigine, levetiracetam, sodium valproate and zonisamide.

Why is this important?

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

Research should include:

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

10.5 Generalised Tonic-Clonic Seizures (GTCS)

10.5.1 Introduction

Tonic- clonic seizures are defined as those where individuals have sudden onset, tonic stiffening, followed by rhythmic, clonic jerking of the limbs. It is the most common presenting seizure type, and an individual may manifest with such a seizure type prior to any underlying syndrome or cause being determined. It is classified as a generalised seizure type, although these seizures may be seen as are of several types in certain syndromes. Furthermore, such an apparent clinical manifestation may be seen if there has been rapid spread of the seizure from a focal source.

10.5.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people experiencing generalised tonic-clonic seizures.

10.5.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for epilepsy in a population experiencing generalised tonic-clonic seizures. The interventions we included in our search were lamotrigine, levetiracetam, topiramate, oxcarbazepine, phenytoin, clobazam, clonazepam, phenobarbitonal, primidone, acetazolamide, sodium valproate, zonisamide and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter. It should be noted that some of the studies from the direct meta-analysis are the same as those in the IPD network meta-analysis.

Matrix of the evidence for monotherapy – adults

Lamotrigine				
Carbamazepine	1[163], 1 IPD NMA [38]			
Phenytoin	1[172], 1 IPD NMA [38]	1[171], 1 IPD NMA [38]		
Sodium valproate	1(Marson, unpublished), 1 IPD NMA [38]	2[171,288], 1 IPD NMA [38]	4[171,176,177,289], 1 IPD NMA [38]	

Oxcarbazepine	1 IPD NMA [38]	1 IPD NMA [38]	1[173], 1 IPD NMA [38]	1[175, 38]				
Topiramate	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1(Marson, unpublished), 1 IPD NMA [38]				
Phenobarbital	1 IPD NMA [38]	1[290], 1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]		
Gabapentin	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	1 IPD NMA [38]	
	LTG	CBZ	PHT	VPA	OXC	TPM	PHB	GBP

Matrix of the evidence for monotherapy – children

Placebo						
Oxcarbazepine						
Phenytoin		1[182]				
Sodium valproate						
Carbamazepine						
	PCB	OXC	PHT	VPA	CBZ	

Matrix of the evidence for Adjunctive therapy

Placebo						
Clobazam	1[291]					
Lamotrigine	1[292]					
Lamotrigine XR	1[293]					
Levetiracetam	1[294]					
Topiramate	2[295,] Barrett (unpublished in HTA)[40]					
	PCB	CLB	LTG	LTG-XR	LEV	TPM

10.5.4 Monotherapy for the treatment of generalised tonic-clonic seizures in adults

10.5.4.1 Lamotrigine versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to 12 month remission occurred significantly more rapidly in participants taking carbamazepine monotherapy compared to participants taking lamotrigine monotherapy although there is uncertainty in the magnitude of clinical effect. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy in the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to withdrawal of treatment. (IPD meta-analysis).

No significant difference between lamotrigine monotherapy and carbamazepine monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to carbamazepine monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.2 Lamotrigine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to 12 month remission occurred significantly more rapidly in participants taking phenytoin monotherapy compared to participants taking lamotrigine monotherapy. (IPD meta-analysis)

Time to first seizure occurred significantly more rapidly in participants taking lamotrigine monotherapy compared to participants taking phenytoin monotherapy. (IPD meta-analysis)

Efficacy – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy in the proportion of seizure free participants. (VERY LOW QUALITY)

There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to first seizure. (VERY LOW QUALITY)

There was no significant difference between lamotrigine monotherapy and phenytoin monotherapy for the time to exit/withdrawal from treatment. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly more participants taking phenytoin monotherapy compared to lamotrigine monotherapy had incidence of the following adverse events:

- somnolence (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)
- asthenia, although there is uncertainty over the magnitude of its clinical effect (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenytoin monotherapy in the incidence of:

- rash (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and phenytoin monotherapy in the proportion of patients who withdrew due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to phenytoin monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.3 Oxcarbazepine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the time to 12 month remission. (IPD meta-analysis).

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the time to exit/withdrawal of treatment. (IPD meta-analysis).

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing oxcarbazepine monotherapy to phenytoin monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.4 Oxcarbazepine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Oxcarbazepine and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing oxcarbazepine monotherapy to sodium valproate monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.5 Phenytoin versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Phenytoin monotherapy is more effective than carbamazepine monotherapy in achieving a greater proportion of seizure-free participants. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the time to 12 month remission. (IPD meta-analysis).

No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing phenytoin monotherapy to carbamazepine monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.6 Phenobarbital versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the time to exit/withdrawal of treatment. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the time to first seizure. (IPD meta-analysis)

Adverse events– statistically non-significant results

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events. (VERY LOW QUALITY)

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the incidence of death (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenobarbital monotherapy to carbamazepine monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- cognitive outcomes

- quality of life outcomes.

10.5.4.7 Phenytoin versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenytoin and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for time to treatment failure. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

Adverse events – statistically significant results

Significantly more participants taking phenytoin monotherapy compared to sodium valproate monotherapy withdrew to due adverse events, although there is uncertainty in the magnitude of clinical effect. (VERY LOW QUALITY)

Adverse events– statistically non-significant results

No significant difference between phenytoin monotherapy and sodium valproate monotherapy for the incidence of the following adverse events:

- gastrointestinal disturbances (VERY LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- death (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenytoin monotherapy to sodium valproate monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- cognitive outcomes
- quality of life outcomes.

10.5.4.8 Sodium valproate versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Sodium valproate and carbamazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly in participants taking carbamazepine monotherapy compared to participants taking sodium valproate monotherapy. (IPD META-ANALYSIS)

Efficacy – statistically non-significant results

No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for time to first seizure. (IPD meta-analysis)

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to carbamazepine monotherapy in patients with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- withdrawal due to adverse events
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

10.5.4.9 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Lamotrigine and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

Economic evidence could not be extracted from the unpublished data for this subgroup of patients.

Evidence statements

Efficacy – statistically significant results

Time to 12-month remission occurred significantly more rapidly on sodium valproate monotherapy compared to lamotrigine monotherapy. (IPD meta-analysis)

Sodium valproate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to first seizure. (IPD meta-analysis)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (LOW QUALITY).

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to exit/withdrawal of allocated treatment at 12 months follow-up (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to treatment failure. (IPD meta-analysis).

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of other adverse events (for full list please see extractions) at 12months follow-up (VERY LOW QUALITY).

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- incidence of other side effects (please see evidence review Appendix L)
- quality of life outcomes.

10.5.4.10 Topiramate versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

Economic evidence could not be extracted from the unpublished data for this subgroup of patients.

Evidence statements

Efficacy – statistically significant results

Time to treatment failure occurred significantly more rapidly in participants taking topiramate monotherapy compared to participants taking sodium valproate monotherapy. (IPD META-ANALYSIS)

Efficacy – statistically non significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure (IPD meta-analysis).

No significant difference between sodium valproate monotherapy and topiramate monotherapy for time to exit/withdrawal of allocated treatment at 12 months follow-up (VERY LOW QUALITY).

No significant difference between sodium valproate monotherapy and topiramate monotherapy for time to 12 month remission. (IPD meta-analysis)

Adverse events - statistically non significant results

No significant difference between topiramate monotherapy and valproate monotherapy at 12 months follow-up in the incidence of:

- tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY)
- other adverse events (for full list please see evidence extractions Appendix L) (VERY LOW QUALITY).

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy

- cognitive outcomes
- quality of life outcomes.

10.5.4.11 Lamotrigine versus Phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Lamotrigine and phenobarbital were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and phenobarbital monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and phenobarbital monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and phenobarbital monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- outcomes relating to quality of life.

10.5.4.12 Lamotrigine versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Lamotrigine and topiramate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Efficacy – statistically significant results

Time to 12-month remission occurred significantly more rapidly on topiramate monotherapy compared to lamotrigine monotherapy. (IPD meta-analysis)

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and topiramate monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.13 Lamotrigine versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Lamotrigine and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and gabapentin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and gabapentin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and gabapentin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.14 Lamotrigine versus Oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Lamotrigine and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between lamotrigine monotherapy and oxcarbazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.15 Topiramate versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and carbamazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and carbamazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between topiramate monotherapy and carbamazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and carbamazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.16 Gabapentin versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and carbamazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.17 Oxcarbazepine versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Oxcarbazepine and carbamazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between oxcarbazepine monotherapy and carbamazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and carbamazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between oxcarbazepine monotherapy and carbamazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.18 Phenobarbital versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and oxcarbazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and oxcarbazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and oxcarbazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.19 Topiramate versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and oxcarbazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.20 Gabapentin versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin and oxcarbazepine were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and oxcarbazepine monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy

- cognitive outcomes
- quality of life outcomes.

10.5.4.21 Phenobarbital versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and gabapentin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and gabapentin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and gabapentin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.22 Topiramate versus gabapentin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and gabapentin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and gabapentin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between topiramate monotherapy and gabapentin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and gabapentin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.23 Topiramate versus Phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate and Phenobarbital were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and phenobarbital monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between topiramate monotherapy and phenobarbital monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and phenobarbital monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.24 Phenobarbital versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital versus phenytoin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and phenytoin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.25 Topiramate versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Topiramate versus phenytoin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and phenytoin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between topiramate monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between topiramate monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.26 Gabapentin versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin versus phenytoin were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and phenytoin monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and phenytoin monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and phenytoin monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.27 Gabapentin versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Gabapentin versus sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between gabapentin monotherapy and sodium valproate monotherapy for time to exit/withdrawal. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between gabapentin monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.4.28 Phenobarbital versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

IPD meta-analysis

Phenobarbital versus sodium valproate were among AEDs included in an individual patient data meta-analysis of AEDs used as monotherapy in adults with newly diagnosed generalised tonic-clonic seizures. The results of this analysis are presented in section 10.5.5.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to exit/withdrawal occurred significantly more rapidly in participants taking sodium valproate monotherapy compared to participants taking phenobarbital monotherapy. (IPD META-ANALYSIS)

Efficacy – statistically non-significant results

No significant difference between phenobarbital monotherapy and sodium valproate monotherapy for time to 12 month remission. (IPD meta-analysis)

No significant difference between phenobarbital monotherapy and sodium valproate monotherapy for time to first seizure. (IPD meta-analysis)

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.5 Individual patient data network meta-analysis as monotherapy for generalised tonic-clonic epilepsy

During the literature review we identified a network meta-analysis of Individual Patient Data (IPD). The IPD was a summary of IPD evidence from randomized controlled trials of eight different AEDs (sodium valproate, phenytoin, lamotrigine, oxcarbazepine, gabapentin, carbamazepine, topiramate and phenobarbital) in monotherapy of generalised tonic-clonic seizures (Tudur Smith et al, 2007)[38]. It should be recognised that this is a network meta-analyses which combines direct and indirect analyses.

The outcomes included in the IPD analysis were time to treatment failure due to inadequate seizure control, intolerable adverse effects or a combination of both; time to 12 month remission from seizures (days from randomisation and end of a period of 12 months without seizures); and time to first seizure after randomisation. It included data from 1552 generalised tonic-clonic participants for time to treatment withdrawal, 1360 generalised tonic-clonic participants for time to 12 month

remission and 1765 generalised tonic-clonic participants for time to first seizure. The following tables show the results for the various outcomes, comparing each AED with the current standard AED, sodium valproate. The significant results are highlighted in bold.

Time to treatment failure

Intervention	Comparator	Hazard ratio
Phenytoin	Sodium valproate	1.03 (0.71 to 1.51)
Lamotrigine	Sodium valproate	1.30 (0.97 to 1.75)
Oxcarbazeine	Sodium valproate	1.50 (0.84 to 2.68)
Gabapentin	Sodium valproate	1.59 (0.22 to 11.50)
Carbamazepine	Sodium valproate	**1.45 (1.07 to 1.96)**
Topiramate	Sodium valproate	**1.74 (1.28 to 2.36)**
Phenobarbital	Sodium valproate	**1.83 (1.07 to 3.13)**

(a) HR<1 VPA worse; HR>1 VPA better

Sodium valproate was found to be significantly better than carbamazepine, topiramate and phenobarbital for time to treatment failure.

Time to 12 month remission

Intervention	Comparator	Hazard ratio
Gabapentin	Sodium valproate	0.26 (0.04 to 1.86)
Phenytoin	Sodium valproate	0.92 (0.72 to 1.18)
Carbamazepine	Sodium valproate	1.00 (0.81 to 1.22)
Topiramate	Sodium valproate	1.09 (0.86 to 1.37)
Oxcarbazepine	Sodium valproate	1.10 (0.73 to 1.67)
Phenobarbital	Sodium valproate	1.28 (0.89 to 1.84)
Lamotrigine	Sodium valproate	**1.41 (1.10 to 1.80)**

(a) HR<1 VPA worse; HR>1 VPA better

Sodium valproate was found to be significantly better than lamotrigine for time to 12 month remission.

Time to first seizure

Intervention	Comparator	Hazard ratio
Phenytoin	Sodium valproate	0.97 (0.77 to 1.23)
Gabapentin	Sodium valproate	1.11 (0.16 to 7.90)
Topiramate	Sodium valproate	1.19 (0.94 to 1.51)
Carbamazepine	Sodium valproate	1.21 (0.99 to 1.47)
Phenobarbital	Sodium valproate	1.28 (0.92 to 1.77)
Oxcarbazepine	Sodium valproate	1.32 (0.90 to 1.94)
Lamotrigine	Sodium valproate	**1.47 (1.20 to 1.80)**

(a) HR<1 VPA worse; HR>1 VPA better

Sodium valproate was found to be significantly better than lamotrigine for time to first seizure.

10.5.6 Monotherapy for the treatment of generalised tonic-clonic seizures in children

10.5.6.1 Oxcarbazepine versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

No significant difference between oxcarbazepine monotherapy and phenytoin monotherapy for the proportion of seizure-free participants. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing oxcarbazepine monotherapy to phenytoin monotherapy in children with generalised tonic-clonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.7 Adjunctive therapy for the treatment of generalised tonic-clonic seizures

10.5.7.1 Clobazam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking clobazam adjunctive therapy were seizure free compared to placebo. However, there is uncertainty about the magnitude of the clinical effect. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing clobazam adjunctive therapy to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.7.2 Lamotrigine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were gaps in the economic evidence base, original economic modelling was undertaken to evaluate AEDs, including lamotrigine, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of the NCGC GTCS model are presented in section 10.5.8.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in lamotrigine adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to placebo. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive therapy and placebo for the proportion of participants having their treatment withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that lamotrigine adjunctive therapy is cost-effective compared to placebo in the treatment of refractory generalised tonic-clonic seizures. This evidence is directly applicable and has minor limitations.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- withdrawal due to lack of efficacy
- cognitive outcomes
- quality of life outcomes.

10.5.7.3 Lamotrigine extended-release versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking lamotrigine extended-release adjunctive therapy were seizure free compared to participants taking placebo. (MODERATE QUALITY)

Significantly more participants taking lamotrigine extended-release adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to participants taking placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine extended-release adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine extended-release adjunctive therapy and placebo for the incidence of the following adverse events:

- headache
- vomiting

10.5.7.4 Levetiracetam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search. As there were gaps in the economic evidence base, original economic modelling was undertaken to evaluate AEDs, including levetiracetam, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of the NCGC GTCS model are presented in section 10.5.8.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking levetiracetam adjunctive therapy were seizure free compared to participants taking placebo. (HIGH QUALITY)

Significantly more participants taking levetiracetam adjunctive therapy achieved at least a 50% reduction in seizure frequency compared to participants taking placebo. (HIGH QUALITY)

Efficacy – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to lack of efficacy. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy and placebo for the proportion of participants having treatment withdrawn due to adverse events. (LOW QUALITY)

No significant difference between levetiracetam adjunctive therapy and placebo for the incidence of the following adverse events:

- nasopharyngitis. (MODERATE QUALITY)
- headache (LOW QUALITY)
- fatigue (LOW QUALITY)
- aggravation of seizures (LOW QUALITY)

Quality of life – statistically non-significant results

No statistically significant difference between levetiracetam adjunctive therapy and placebo in achieving a greater improvement in the quality of life. (LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that levetiracetam adjunctive therapy is cost-effective compared to placebo in the treatment of refractory generalised tonic-clonic seizures. However, lamotrigine adjunctive therapy is less costly and more effective than levetiracetam adjunctive therapy. This evidence is directly applicable and has minor limitations.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes

10.5.7.5 Topiramate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [181] was identified in the economic literature search and included in the evidence review. As there were still gaps in the economic evidence base, original economic

modelling was undertaken to evaluate AEDs, including topiramate, used in the treatment of patients with refractory generalised tonic-clonic seizures. Full results of this study and the NCGC GTCS model are presented in section 10.5.8.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking topiramate adjunctive therapy compared to placebo achieved at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo in achieving a greater proportion of seizure-free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant

No significant difference between topiramate adjunctive therapy and carbamazepine monotherapy for the proportion of participants who withdrew due to adverse events (VERY LOW QUALITY)

No statistically significant difference between topiramate adjunctive therapy and placebo for the incidence of the following adverse events:

- somnolence (VERY LOW QUALITY)
- anorexia (VERY LOW QUALITY)
- difficulty with memory (VERY LOW QUALITY)
- nervousness (VERY LOW QUALITY)
- psychomotor slowing (VERY LOW QUALITY)
- upper respiratory tract infection (VERY LOW QUALITY)
- pharyngitis (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- speech disorders and related speech problems (VERY LOW QUALITY)
- abdominal pain (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)
- insomnia (VERY LOW QUALITY)
- aggressive reaction (VERY LOW QUALITY)
- confusion (VERY LOW QUALITY)

Cost-effectiveness

Two economic evaluations based on cost-utility analyses show that topiramate adjunctive therapy is more effective and more costly than placebo, with incremental cost-effectiveness ratios of £34,417 and £75,723 per QALY gained, respectively. The first estimate is from a partially applicable study with potentially serious limitations. In the second analysis, topiramate adjunctive therapy was dominated by lamotrigine adjunctive therapy and extendedly dominated by levetiracetam adjunctive therapy. This analysis is directly applicable and has minor limitations.

10.5.8 Health economic evidence for AEDs used as adjunctive therapy in adults with refractory generalised tonic-clonic seizures

One study[181] assessing the cost-effectiveness of topiramate used as adjunctive therapy in patients with refractory generalised tonic-clonic seizures was identified in the economic literature search and included in the economic evidence review. As there were still gaps in the evidence base, an original economic model was developed to compare AEDs used as adjunctive therapy in patients with refractory generalised tonic-clonic seizures. This was based on evidence included in the clinical review[292,294,295]. See appendix S for full details and results of modelling.

Economic study characteristics

Table 18: Adjunctive therapy for patients with refractory generalised tonic-clonic seizures - Economic study characteristics

Study	Limitations	Applicability	Other Comments
NCGC GTCS model (see appendix S for details)	Minor limitations	Directly applicable	Decision analytic model; 15-year time horizon; comparators included monotherapy (placebo), lamotrigine, topiramate and levetiracetam; effectiveness data from studies included in clinical review[292,294,295]
Hawkins 2005[181]	Potentially serious limitations(a)	Partially applicable (b, c)	Decision analytic model; 15-year time horizon; effectiveness data from Barret 1998[296] and Biton 1999[295].

(a) Unit cost estimates are from 2002/03, and since then, unit cost of topiramate has reduced and may change conclusions of the cost-effectiveness analysis.
(b) Analysis includes only two comparators of interest
(c) Costs discounted 6% per annum; effects discounted 1.5% per annum

Economic study results – NCGC GTCS model

Table 19: Adjunctive therapy for patients with refractory generalised tonic-clonic seizures – Results of NCGC GTC model

AED	Total cost (£) per patient	Total effect (QALYs) per patient	ICER (£/QALY)	Uncertainty
Placebo	£6,248	7.515		At thresholds of £20K and £30K/QALY, monotherapy (placebo) has a 0% probability of being optimal. If LTG is excluded from the analysis: monotherapy has 24.95% and 5% probability of being optimal at £20K and £30K /QALY respectively.
LTG	£6,614	7.761	£1,488	At a threshold of £20K and £30K/QALY, LTG has a 98.74% and 96.16% probability of being optimal, respectively.
LEV	£9,556	7.738	Dominated	At thresholds of £20K and £30K/QALY, LEV has a 1.26% and 3.84% probability of being optimal, respectively.

AED	Total cost (£) per patient	Total effect (QALYs) per patient	ICER (£/QALY)	Uncertainty
				If LTG is excluded from the analysis: ICER=£14,834 and has 74.86% and 94.83% probability of being optimal at £20K and £30K /QALY, respectively.
TPM	£9,807	7.562	Dominated	At thresholds of £20K and £30K/QALY, TPM has a 0% probability of being optimal. If LTG is excluded from the analysis: TPM is extendedly dominated by LEV and has 0.19% and 0.18% probability of being optimal at £20K and £30K/QALY, respectively. If LTG is excluded and only non-proprietary costs for TPM are used, TPM is extendedly dominated by LEV and has a <2% chance of being optimal at £20K and £30K /QALY.

Evidence statements

Evidence from one cost-effectiveness analysis indicates that lamotrigine is the most cost-effective adjunctive AED for the treatment of refractory generalised tonic-clonic seizures. This evidence is directly applicable and has minor limitations.

Evidence from one cost-effectiveness analysis indicates that levetiracetam is more costly and less effective than lamotrigine in the treatment of refractory generalised tonic-clonic seizures. However, if lamotrigine is not a clinically appropriate option, levetiracetam is very likely to be considered cost-effective given a threshold of £20,000 per QALY. This evidence is directly applicable and has minor limitations.

Evidence from one cost-effectiveness analysis indicates that topiramate is more costly and less effective than lamotrigine and is extendedly dominated by levetiracetam when lamotrigine is not a clinically appropriate drug option. This evidence is directly applicable and has minor limitations.

Economic study results – Hawkins 2005[181]

Table 20: Adjunctive therapy for patients with refractory generalised tonic-clonic seizures – Results of Hawkins 2005[181]

AED	Total cost (£) per patient	Total effect (QALYs) per patient	ICER (£/QALY)	Uncertainty
Placebo	£5,064	8.737		At threshold of £30K /QALY, monotherapy (placebo) has 59% probability of being optimal
TPM	£7,471	8.807	£34,417	At threshold of £30K/QALY, topiramate has a 41% probability of being optimal

Evidence statements

Evidence from one cost-effectiveness analysis indicates that topiramate is more costly and more effective than continued monotherapy, but with an incremental cost-effectiveness ratio greater than £20,000 and £30,000 per QALY gained, it is unlikely to be considered cost-effective in this patient group. This evidence is partially applicable and has potentially serious limitations.

10.5.9 New recommendations and link to evidence

First-line treatment in children, young people and adults with newly diagnosed generalised tonic-clonic (GTC) seizures

Recommendation	**90. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed GTC seizures. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]** **91. Offer lamotrigine if sodium valproate is unsuitable. If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures. [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure freedom and adverse effects were considered to be the most important outcomes. Time to withdrawal, time to 12 month remission and time to first seizure were also considered important.
Trade off between clinical benefits and harms	In adults, there was no significant difference in the proportion of participants achieving seizure freedom between sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. There were few significant differences in the direct evidence for efficacy and for most comparisons in the IPD analyses. However sodium valproate was significantly better than phenobarbital, topiramate and carbamazepine for time to withdrawal. Phenytoin and sodium valproate were significantly better than lamotrigine for time to first seizure. Phenytoin, carbamazeine, sodium valproate and topiramate were significantly better than lamotrigine for time to 12 month remission. Based on the evidence for a population with generalised tonic-clonic seizures only there was no significant difference between lamotrigine, sodium valproate and topiramate in terms of time to treatment failure or time to first seizure. The GDG consensus opinion was that there is a tendency for drugs such as carbamazepine and oxcarbazepine to exacerbate certain seizures types such as myoclonic and absence seizures. Therefore, they concluded that although there is evidence to support the role of carbamazepine and oxcarbazepine in the treatment of generalised tonic-clonic seizures, they should only be considered once other seizure types have had time to present following initiation of first-line drugs. The GDG considered that due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, it is not a drug of first choice where other drugs are as effective. Phenytoin was shown to have efficacy but the GDG considered it to have a very high adverse events profile. The long term effects such as gum hypertrophy, coursing of facies, hirsuitism, cerebellar atrophy would make it unfavourable to use long term. The GDG also considered the pharmacokinetics to be unpredictable which

	makes dosing difficult. Sodium valproate and high dose lamotrigine are associated with increased risk of neural tube and other defects and so the women of child-bearing age should be informed of such risks. The GDG considered that the benefits of reduction of seizures outweighed the adverse effects.
Economic considerations	No economic evidence was identified in the literature and no economic evaluation was undertaken to inform the cost-effectiveness of first line AEDs used to treat newly diagnosed patients experiencing generalised tonic-clonic seizures. The GDG felt that an extrapolation from the SANAD study population with generalised epilepsies to a population with generalised tonic-clonic seizures was appropriate and that the relative cost-effectiveness of sodium valproate was unlikely to be different between these groups. Sodium valproate emerged as the drug most likely to be cost-effective in the cost per seizure avoided analysis conducted as part of the SANAD trial[161]. Greater weight was given to this analysis as the reduction in seizure frequency, particularly of generalised tonic-clonic seizures, is considered to be the most important clinical outcome. The published economic evidence for the cost effectiveness of lamotrigine in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and is also likely to be considered cost-effective.
Quality of evidence	Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power of the direct studies particularly with regard to adverse events. The overall quality of direct evidence was very low with poor reporting of randomisation methods, allocation concealment and many studies were unblinded. There was a high drop-out rate in the majority of studies. The time to event data came from a network meta-analysis of individual patient data.
Other considerations	During the literature review we identified an analysis of Individual Patient Data (IPD) which included data from eight IPD Cochrane reviews and data from the SANAD trial of eight different AEDs (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, sodium valproate and topiramate) The GDG considered the IPD analysis in the decision making process alongside the direct evidence. Most of the evidence for the GTCS review came from the IPD analysis, this difference occurred because the IPD analysis subgrouped the individual patient data into specific seizure types whereas the direct evidence was based on how the authors had chosen to categorise and present the data. Sodium valproate inhibits the metabolism of lamotrigine and this must to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium

	valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in the lamotrigine dose. The GDG is aware that levetiracetam is widely used in current practice as a first-line monotherapy in the treatment of newly diagnosed generalised tonic-clonic seizures, particularly when sodium valproate is unsuitable. There was much debate as to whether levetiracetam should be recommended alongside or in preference to lamotrigine, especially considering lamotrigine's potential to exacerbate myoclonic seizures that may or may not have previously presented. However, the GDG's final decision not to recommend levetiracetam as first line monotherapy in this group of patients is in accordance with NICE methodology which states that 'use for an indication for which the product does not have a marketing authorization may be recommended if there is clear evidence to support this.' Levetiracetam is not currently licensed as monotherapy in the treatment of generalised epilepsies and no randomised controlled trial evidence was identified to demonstrate its effectiveness compared to alternative drugs. Furthermore, in the absence of such evidence it is impossible to measure levetiracetam's relative cost-effectiveness compared to other demonstrably cost-effective AEDs used to treat tonic-clonic seizures. Consequently, levetiracetam is recommended as adjunctive therapy, where evidence is available to demonstrate its clinical and cost-effectiveness. The GDG considered it important to direct users of the guideline to the recommendations for the treatment of myoclonic seizures and juvenile myoclonic epilepsy where other drugs, including topiramate and levetiracetam, may be considered if sodium valproate or lamotrigine are unsuitable.

Recommendation	**92. Consider carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure-freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	In adults, there was no significant difference in seizure freedom between sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. In children there was no difference between sodium valproate and carbamazepine.
Economic considerations	There were few significant differences in the direct evidence for efficacy and for most comparisons in the IPD analyses. Sodium valproate was significantly better than carbamazepine for time to withdrawal. Carbamazepine was significantly better than lamotrigine for time to 12 month remission.
Quality of evidence	Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power of studies particularly with regard to adverse events. The overall quality of evidence was very low with poor reporting of randomisation methods, allocation concealment and many studies were unblinded. There was a high drop-out rate in the majority of studies.
Other considerations	During the literature review we identified an analysis of Individual Patient Data (IPD) which included data from eight IPD Cochrane reviews and data from the SANAD trial of eight different AEDs (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, sodium valproate and topiramate) We used the IPD analysis as supplementary evidence to the direct evidence. The GDG considered the IPD analysis in the decision making process alongside the direct evidence. The GDG consensus opinion reflects widespread clinical experience that drugs such as carbamazepine and oxcarbazepine may exacerbate certain seizures types, and specifically myoclonic and absence seizures. Therefore, they concluded that although there is evidence to support the role of carbamazepine and oxcarbazepine in the treatment of generalised tonic-clonic seizures, they should only be considered once other seizure types have had time to present following initiation of first-line drugs.

Adjunctive treatment in children, young people and adults with newly diagnosed GTC seizures

Recommendation	**93. Offer clobazam*, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with GTC seizures if first-line treatments (see recommendations 90, 91 and 92) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The most important outcomes were adverse effects and 50% reduction in seizure frequency.
Trade off between clinical benefits and harms	Lamotrigine, levetiracetam and topiramate as adjunctive therapies all significantly reduced seizure frequency by at least 50% when compared to placebo. There was significantly more seizure freedom with clobazam and levetiracetam compared to placebo but lamotrigine and topiramate showed no difference compared to placebo. There was no significant difference for any adverse event, withdrawal due to adverse events or lack of efficacy for lamotrigine, levetiracetam and topiramate adjunctive therapies when compared to placebo.
Economic considerations	The GDG considered the evidence from the economic evaluation undertaken for the guideline in which lamotrigine emerged as a very cost-effective adjunctive therapy in patients experiencing refractory generalised tonic-clonic seizures. If lamotrigine had been tried previously, levetiracetam was also likely to be a cost-effective adjunctive AED. Topiramate was not shown to be cost-effective, but in the event that other alternatives fail to produce the desired reduction in seizure frequency, the GDG felt that it should be considered. Clobazam was not evaluated as part of the cost-effectiveness analysis because the clinical studies did not report all outcomes necessary for inclusion. However, the GDG considered that its effectiveness compared to placebo and its small unit cost is likely to make it cost-effective.
Quality of evidence	Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power in the studies particularly with regard to side-effects. The overall quality of evidence was low: some had no details of randomisation or allocation concealment, high drop-out rate or a very small sample size.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Other considerations	There is a pharmacodynamic interaction between levetiracetam and carbamazepine and between lamotrigine and carbamazepine so side effects may be enhanced. Sodium valproate inhibits the metabolism of lamotrigine and this must be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose. Care should be taken when withdrawing clobazam with a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. Topiramate may affect phenytoin levels.

Recommendation	**94. If there are absence or myoclonic seizures, or if JME is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Reduction in seizures and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that absence and myoclonic seizures can be aggravated by these medications. Given that these two seizure types may accompany generalised tonic-clonic seizures, the GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	We found no evidence for these drugs in relation to generalised tonic-clonic seizures. This recommendation was based on GDG consensus.
Other considerations	None.

10.6 Absence Seizures

10.6.1 Introduction

Absence seizures are characterised by paroxysmal episodes behavioural arrest with loss of consciousness, associated with generalised spike and wave activity on EEG. Typical absences seizures

are abrupt in onset and offset, short in duration (usually <10 seconds), and occur frequently. Synchronous spike wave activity is seen on the EEG at a frequency of 3Hz or above. Such are seen as part of childhood onset epilepsy syndromes such as childhood absence epilepsy and juvenile absence epilepsy. Atypical absences may not be as abrupt in onset or offset, are typically longer in duration (>20 seconds), and consciousness may not be totally lost. Further the EEG during the attack is more heterogeneous with irregular slower spike wave activity (1-2Hz). Such may be seen in isolation, or associated with other seizure types as part of an epilepsy syndrome eg Lennox Gastaut syndrome.

10.6.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people with myoclonic seizures.

10.6.3 Matrix of the evidence

For details on the matrix of the evidence please refer to the evidence review for IGE in section 10.13.

10.6.4 AEDs for the treatment of absence seizures

Clinical evidence

For details on the clinical evidence please refer to the evidence review for IGE in section 10.13. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

10.6.5 New recommendations and link to evidence

First-line treatment in children, young people and adults with absence seizures

Recommendation	**95. Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence seizures. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that the different side effect profiles of sodium valproate and ethosuximide could not determine which one of these drugs be used first, although there may be individual factors that may determine the choice of one drug over the other. Significantly more patients on valproate showed difficulties in attention. Caution should be used with sodium valproate in girls of child bearing potential.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. At the time the GDG considered the evidence, there were significant cost differences between ethosuximide capsules (£0.68 per 250 mg) and ethosuximide syrup (£0.108 to £0.165 per 250 mg). According to the Prescription Cost Analysis of 2008, 99.7% of ethosuximide prescriptions were for syrup. When ethosuximide syrup is prescribed, the daily unit costs of ethosuximide and sodium valproate are very comparable. On this basis the GDG considered that clinical judgement and patient choice should guide the decision for which of the likely cost-effective drugs to offer.
Quality of evidence	The evidence base for this recommendation was retrieved from a double blinded study of a very good quality, a double-blinded of unclear/low quality and from two unblinded studies.
Other considerations	The GDG considered that the data available for childhood absence epilepsy can be extrapolated to those individuals with juvenile absence epilepsy, and also to those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.

Recommendation	**96. Offer lamotrigine* if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that the side effect profile of lamotrigine was more favourable, but its efficacy was less favourable, when compared with ethosuximide and sodium valproate.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. The GDG considered that at recommended daily doses lamotrigine, sodium valproate and ethosuximide syrup have broadly similar unit costs, but that lamotrigine was less effective than sodium valproate and ethosuximide in this population. But if sodium valproate and/or ethosuximide do not produce the clinical benefit desired, the GDG felt that lamotrigine was a potentially cost-effective alternative.
Quality of evidence	The evidence base was retrieved from a double blinded study of very good quality and from two unblinded studies.
Other considerations	The GDG considered that the data available for CAE can be extrapolated to those individuals with JAE, and those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Adjunctive treatment in children, young people and adults with absence seizures

Recommendation	**97. If two first-line AEDs (see recommendations 95 and 96) are ineffective in children, young people and adults with absence seizures, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine* or sodium valproate. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom, reduction in seizure frequency and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that if at least two of the first line AEDs have failed to produce the desired effect (seizure freedom), then it is appropriate to try a well tolerated combination of two of them. Although there is no evidence in this population specifically, GDG experience is that any of the three can be safely combined and given their effectiveness as individual drugs, the expectation is that they are effective in combination. Caution should be used with sodium valproate in girls of child bearing potential.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used as monotherapy or adjunctive therapy to treat CAE, JAE or generalised absence seizures. There was no evidence to suggest that any specific combination of ethosuximide, lamotrigine and sodium valproate is better than another. Any combination is expected to be broadly similar in terms of cost as well. Therefore, the GDG considered that clinical judgement and patient choice should guide the decision for which of the likely cost-effective AED combinations to offer.
Quality of evidence	The evidence base for this recommendation was extrapolated from the evidence for each of these drugs as monotherapy in newly diagnosed absence seizures and was supported by GDG consensus.
Other considerations	The GDG considered that the data available for childhood absence epilepsy can be extrapolated to those individuals with juvenile absence epilepsy, and also to those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**98. If adjunctive treatment (see recommendation 97) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam, levetiracetam*, topiramate* or zonisamide*. [new 2012]**
Relative values of different outcomes	Reduction in seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	The GDG consensus was that clobazam, clonazepam, topiramate or zonisamide were possible alternatives in accordance with tertiary epilepsy care. The GDG considered it important to mention these drugs as potential options to offer to patients between the time of referral to and consultation with a tertiary specialist. It was thought that these are some of the drugs that a tertiary specialist might use, basing the decision on clinical experience treating patients with refractory absence seizures. There was no difference found for topiramate and sodium valproate for time to first seizure from sodium valproate but topiramate had a shorter time to withdrawal. Due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, the GDG felt it is not a drug of first choice where other drugs are suitable.
Economic considerations	The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome. With regard to the specific drugs listed here, there were no economic evaluations available to inform the GDG on the cost-effectiveness of clobazam, clonazepam, topiramate or zonisamide.
Quality of evidence	There was no evidence available for absence seizures for clobazam, clonazepam and zonisamide so these drugs were added to this recommendation based on GDG clinical expertise. There was limited evidence available for topiramate in absence seizures from a large unblinded pragmatic trial.
Other considerations	Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**99. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that absence seizures can be aggravated by these medications. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however, their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	There is no evidence of benefit on use of these medications

10.7 Myoclonic Seizures

10.7.1 Introduction

Myoclonic seizures are defined as sudden, brief involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable limb location. Myoclonic seizures are seen as part of several epilepsy syndromes eg juvenile myoclonic epilepsy, Dravet syndrome. In these circumstances treatment should be considered in the context of the diagnosed syndrome rather than individual seizure types. However there are a variety of static encephalopathies not fulfilling criteria for specific epilepsy syndromes, where myoclonic seizures are the major if not only seizure type. Further there are a number of progressive myoclonic epilepsies for which specific treatment of myoclonus may require consideration.

10.7.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included people with myoclonic seizures.

10.7.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for myoclonic seizures. The following interventions were included in our search: clobazam, clonazepam, lamotrigine, levetiracetam, piracetam, sodium valproate, topiramate and zonisamide. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo									
Lamotrigine									
Levetiracetam	1 [297]								
Clobazam									
Clonazepam									
Piracetam									
Topiramate									
Sodium Valproate		1 [165]					1 [298]		
Zonisamide									
	Pla	LTG	LEV	CLB	CLN	PRC	TPM	VPA	ZNS

10.7.4 Monotherapy for the treatment of myoclonic seizures

10.7.4.1 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of seizure free participants (VERY LOW QUALITY).

There was no significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to lack of efficacy (VERY LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants withdrawn due to adverse events (VERY LOW QUALITY).

No statistically significant difference between lamotrigine and sodium valproate for incidence of the following adverse events:

- erythematous rash (VERY LOW QUALITY)
- weight increase (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with myoclonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- outcomes relating to quality of life.

10.7.4.2 Topiramate monotherapy/adjunctive therapy versus sodium valproate monotherapy/adjunctive therapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for 50% reduction in seizure frequency. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with myoclonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- outcomes relating to quality of life.

10.7.5 Adjunctive therapy for the treatment of myoclonic seizures

10.7.5.1 Levetiracetam adjunctive therapy versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants receiving levetiracetam adjunctive were myoclonic seizure-free compared to placebo. However, there is uncertainty in the magnitude of the clinical effect (LOW QUALITY).

Significantly more participants receiving levetiracetam adjunctive achieved 50% or above reduction in seizure frequency compared to placebo (MODERATE QUALITY).

Adverse events – statistically non significant results

There is no significant difference between the levetiracetam adjunctive group and the placebo group on the incidence of:

- somnolence (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

Quality of life - statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy had experienced improvement in health related quality of life compared to placebo (MODERATE QUALITY).

Cost-effectiveness

No economic evidence comparing levetiracetam adjunctive therapy to placebo in a population of patients with myoclonic seizures was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive effects.

10.7.6 New recommendations and link to evidence

First-line treatment in children, young people and adults with myoclonic seizures

Recommendation	**100. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed myoclonic seizures, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG placed most importance on efficacy as measured by seizure freedom, time to first seizure and time to withdrawal and adverse events.
Trade off between clinical benefits and harms	The evidence for monotherapy in the treatment of patients with myoclonic seizures is very limited, based on unblinded studies with very small samples or subgroups comparing only lamotrigine or topiramate to sodium valproate. Therefore the GDG used evidence extrapolated from juvenile myoclonic epilepsy to make this recommendation. The evidence comparing sodium valproate and lamotrigine or topiramate in a population experiencing myoclonic seizures was not powered to show a difference in terms of effectiveness or tolerability. Results from an unpublished subgroup analysis (SANAD datasests) for juvenile myoclonic epilepsy showed that sodium valproate was more effective than lamotrigine although there was no significant difference observed in terms of treatment failure. Sodium valproate is the most effective drug for treating IGE, but it has certain disadvantages. The risk of teratogenicity associated with the use of sodium valproate use is significant, particularly at higher doses, so caution is advised in the use of valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of sodium valproate should be reviewed and options discussed. Although there was evidence for lamotrigine in this group, the GDG considered it an inappropriate treatment option due to its inefficacy and possible risk of exacerbation of myoclonic seizures. Exacerbation of seizures was not found in the study for myoclonic seizures but this may be because the adverse event data was derived from the overall generalised epilepsy group, and was not specific to the myoclonic seizures subgroup, who accounted for 22.2% of the generalised epilepsy group.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat patients experiencing myoclonic seizures. However, as in the formulation of recommendations for the treatment of juvenile myoclonic epilepsy (JME), the GDG drew from the cost-effectiveness evidence for sodium valproate in idiopathic generalised epilepsy as a whole. On this basis, they put greater emphasis on the cost per seizure avoided analysis from SANAD because reduction of seizure frequency is

	considered to be the most important clinical outcome.
Quality of evidence	The evidence for myoclonic seizures was limited. Two unblinded studies of very low quality evidence were included with no details on randomisation and no allocation concealment. One was a small subgroup from a very small pilot study of juvenile myoclonic epilepsy and the other was a small subgroup which the authors did not statistically compare due to the size and imbalance of distribution. This recommendation was based on evidence for monotherapy extrapolated from JME populations. The JME data mainly came from a large pragmatic unblinded trial (SANAD).
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

First-line treatment in children, young people and adults with myoclonic seizures

Recommendation	**101. Consider levetiracetam* or topiramate* if sodium valproate is unsuitable or not tolerated. Be aware that topiramate has a less favourable side-effect profile than levetiracetam and sodium valproate. [new 2012]**
Relative values of different outcomes	The GDG placed greater importance on efficacy as measured by seizure freedom, time to first seizure and time to withdrawal and adverse events.
Trade off between clinical benefits and harms	Topiramate can be considered, but be aware of the less favourable side effect profile. The evidence was limited for topiramate in this group and so evidence was extrapolated from the JME review which found no difference between topiramate and sodium valproate for efficacy or adverse events. It is the GDG consensus opinion that topiramate has not been shown to be effective in IGE with photosensitivity. There are limited data on the safety of topiramate in pregnancy. At present the risk in pregnancy appears overall to be similar to lamotrigine. Topiramate, particularly at higher doses, may reduce the efficacy of the combined oral contraceptive. Finally, due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, the GDG felt it is not a drug of first choice where other drugs are suitable. At the time of writing this guideline levetiracetam is not currently licensed for monotherapy in the UK but it is effective as adjunctive therapy in myoclonic seizures and has the advantage of having no significant reported interactions with other medications. Further, the GDG experience is that it has a very favourable side effect profile. It is also the only other AED that has been demonstrated to be effective in the suppression of photoparoxysmal response (in a phase II trial of 12 photosensitive patients by Kasteleijn-Nolst in 1996). The GDG decided to recommend off-label use of levetiracetam for myolonic seizures as the evidence for efficacy and tolerability in adjunctive therapy concurred with their clinical experience of its use in monotherapy. Additionally, the GDG felt that there was a need for more options to be available to treat patients with myoclonic seizures given the adverse effect profile for alternative drugs for which there is evidence. At the time of writing the guideline, there are insufficient data to judge the safety of levetiracetam in pregnancy.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Economic considerations	The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, topiramate may be a cost-effective alternative. The published economic evidence for the cost effectiveness of topiramate in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that topiramate has the highest total cost but that it is likely to be considered cost-effective. There is currently no evidence on which to assess the cost-effectiveness of levetiracetam as a monotherapy in patients experiencing myoclonic seizures. In the absence of any applicable economic evidence, the GDG considered the cost-effectiveness results of levetiracetam as a monotherapy in a population with focal epilepsy where it was more effective than topiramate and also had a slightly lower total cost over the entire 15-year time horizon. In addition, the GDG looked to the results of the decision model undertaken to evaluate adjunctive therapies in a population with refractory generalised tonic-clonic seizures, where levetiracetam was also less costly and more effective than topiramate. On the assumption that levetiracetam is at least as effective as topiramate in the treatment of myoclonic seizures, the GDG concluded that, as observed in other populations, it was likely to represent reasonable value to the NHS when sodium valproate is an unsuitable treatment option. Research into both the effectiveness and cost-effectiveness of levetiracetam as a monotherapy in this population is essential to reduce the substantial uncertainty in this decision.
Quality of evidence	The data for myoclonic seizures was limited therefore the evidence was extrapolated from JME and adjunctive therapy for myoclonic seizures and GDG clinical expertise. The JME data mainly came from a large pragmatic unblinded trial (SANAD). The levetiracetam adjunctive data came from a good quality double blinded study with all participants having myoclonic seizures.
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Adjunctive treatment in children, young people and adults with myoclonic seizures

Recommendation	**102. Offer levetiracetam, sodium valproate or topiramate* as adjunctive treatment to children, young people and adults with myoclonic seizures if first-line treatments (see recommendations 100 and 101) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	At least of 50% seizure reduction and adverse effects were considered the most important outcomes.
Trade off between clinical benefits and harms	Levetiracetam is effective as adjunctive therapy in myoclonic seizures and has the advantage of no significant interactions with other medications. There are insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline. There was no evidence for topiramate as adjunctive therapy but there was some evidence extrapolated for monotherapy from JME which found it to be effective and the GDG thought it would also be effective as adjunctive therapy.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of levetiracetam or topiramate as treatments specifically in patients experiencing refractory myoclonic seizures. The GDG considered the clinical evidence for adjunctive levetiracetam in a population with JME which shows it to be even more effective compared to placebo than in a population with primary generalised tonic-clonic seizures. On that basis, the GDG felt that the cost-effectiveness of adjunctive levetiracetam was likely to be the same or better than in the analysis conducted for patients with primary generalised tonic-clonic seizures, summarised in section 10.5.8 and detailed in appendix S. In the same analysis, topiramate was not shown to be cost-effective, but in the event that adjunctive levetiracetam fails to produce the desired reduction in seizure frequency, the GDG felt that it could be considered.
Quality of evidence	The overall quality grading for levetiracetam was low to moderate quality. There was only one double-blind study of IGE with myoclonic seizures for levetiracetam versus placebo. There was no evidence available for topiramate adjunctive therapy but JME data for topiramate mainly came from a large pragmatic unblinded trial (SANAD).
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**103. If adjunctive treatment (see recommendation 102) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam, piracetam or zonisamide*. [new 2012]**
Relative values of different outcomes	Reduction in seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	The GDG consensus was that clobazam, clonazepam, piracetam or zonisamide were possible alternatives in accordance with tertary epilepsy care. The GDG considered it important to mention these drugs as potential options to offer to patients between the time of referral to and consultation with a tertiary specialist. It was thought that these are some of the drugs that a tertiary specialist might use, basing the decision on clinical experience treating patients with refractory generalised seizure types.
Economic considerations	The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome. With regard to the specific drugs listed here, there were no economic evaluations available to inform the GDG on the cost-effectiveness of clobazam, clonazepam, piracetam or zonisamide.
Quality of evidence	There was no evidence available for myoclonic seizures or JME for these drugs so this recommendation was based on GDG clinical expertise.
Other considerations	Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**104. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that myoclonic seizures can be aggravated by these medications. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however, their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	There is no evidence of benefit on use of these medications

10.8 Tonic or atonic seizures

10.8.1 Introduction

Tonic and atonic seizures are generalised seizures that on occurrence may cause an individual to fall, so called 'drop attacks'. Tonic seizures involve abrupt generalised muscle stiffening. They usually last less than a minute and recovery is rapid. EEG at the time of the seizure demonstrates low voltage fast activity. Seizures of this type may be seen in isolation, or more characteristically are seen with other seizure types as part of an epilepsy syndrome. Atonic seizures are characterised by sudden onset of loss of muscle tone in association with an EEG change, polyspikes and wave, or falttening, or low-voltage fast activity. It is unsual to see this seizure type in isolation; more typically it is seen in association with other seizure types as part of an epilepsy syndrome. Both seizure types are part of the electroclinical picture seen in Lennox Gastaut syndrome.

10.8.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with tonic or atonic seizures.

10.8.3 Matrix of the evidence

No clinical or cost-effectiveness evidence was found for adults and children with tonic or atonic seizures.

10.8.4 New recommendations and link to evidence

First-line treatment in children, young people and adults with tonic or atonic seizures

Recommendation	***105.*** **Offer sodium valproate as first-line treatment to children, young people and adults with tonic or atonic seizures. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	Seizure freedom, at least 50% reduction in seizure frequency (all seizures and drop attack seizures) and tolerability, as measured by withdrawal due to adverse events, were considered to be the most important outcomes.
Trade off between clinical benefits and harms	The potential benefits of reducing seizures need to be balanced against the potential for adverse effects. No evidence was found for adults and children experiencing tonic or atonic seizures. Evidence was extrapolated from the Lennox-Gastaut evidence review where drugs were assessed on the outcome of reduction in 'drop attacks' (drop seizures). No RCT evidence was retrieved on sodium valproate in this area. However, there is evidence that sodium valproate is effective in reducing other generalised seizures (tonic-clonic, clonic and myocolonic) and the GDG opinion was that this evidence could be extrapolated to this group.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat patients with tonic or atonic seizures. However, the GDG considered that at initial presentation, treatment choice is influenced by the predominant seizure type. In this situation most tonic and atonic seizures are likely to represent a generalised, rather than focal seizure type. Therefore, the GDG extrapolated the evidence of cost-effectiveness for sodium valproate from the results of SANAD, presented in section 10.5.4.
Quality of evidence	We found no RCTs in newly-diagnosed patients or that compared sodium valproate with another antiepileptic drug. We also found no RCTs that compared two drugs as add-on treatment. The recommendation is based on extrapolated evidence from Lennox Gastaut syndrome and GDG consensus opinion.
Other considerations	There is no specific data for first line treatment in children and young people with tonic or atonic seizures. Thus, data has been extrapolated from the Lennox-Gastaut population. It is recognised that at the time epilepsy is diagnosed, it may not be possible to identify the specific epilepsy syndrome. The choice of AED will then be made on the predominant seizure type (or types).

Adjunctive treatment in children, young people and adults with tonic or atonic seizures

Recommendation	***106.*** **Offer lamotrigine* as adjunctive treatment to children, young people and adults with tonic or atonic seizures if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2012]**
Relative values of different outcomes	Seizure freedom, at least 50% reduction in seizure frequency (all seizures and drop attack seizures) and tolerability, as measured by withdrawal due to adverse events, were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Evidence was extrapolated from the Lennox-Gastaut evidence review, where studies evaluated response in 'drop attacks'. Lamotrigine adjunctive treatment is more effective in reducing 'drop attacks' by at least 50% and has a similar side effects profile when compared to placebo.
Economic considerations	The treatment of tonic or atonic seizures, similarly to Lennox-Gastaut syndrome generally requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. The GDG considered the results of two cost-effectiveness analyses from the Lennox Gastaut review, wherein lamotrigine was less costly and more effective than standard monotherapy in terms of reducing the frequency of all seizures and drop attack seizures and less costly and more effective than topiramate in reducing of all seizure types and produced more QALYs. The analyses had some potentially serious limitations, but the GDG considered that lamotrigine is a relatively inexpensive AED and was shown to be effective in terms of reducing the number of 'drop attacks' and tonic-clonic seizures in the clinical review. It was also associated with fewer side effects than topiramate and rufinamide. On this basis, the GDG judged it the AED most likely to be considered cost-effective.
Quality of evidence	Evidence was extrapolated from the Lennox-Gastaut evidence review. The two studies included for the comparison of lamotrigine adjunctive versus placebo were of low quality due to serious limitations in the study design as both of them had no information on randomisation and no allocation concealment.
Other considerations	None.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	***107.*** **Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 106) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide* and topiramate*. [new 2012]**
Relative values of different outcomes	Should the specific epilepsy syndrome diagnosis not be certain following a trial of two medications, assessment by tertiary epilepsy specialist is recommended to discuss syndrome, cause and further drug management. Seizure freedom, at least 50% reduction in seizures and drop attack seizure frequency, as well as withdrawal due to adverse events were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Evidence was extrapolated from the Lennox-Gastaut evidence review. If adjunctive treatment is not tolerated or ineffective further treatment may be successful but the GDG felt that this should be discussed with a tertiary epilepsy specialist. The balance between reducing seizures (which may be injurious and debilitating) and adverse effects needs to be considered when choosing drug treatment. Rufinamide and topiramate adjunctive treatments were more effective in reducing frequency of all seizures by at least 50%. Rufinamide was also more effective in reducing the frequency of drop attack seizures by at least 50%. However, both rufinamide and topiramate had worse side-effect profiles compared to placebo.
Economic considerations	The treatment of tonic and atonic seizures, similarly to Lennox-Gastaut syndrome may requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. 'Drop-attacks' can be dangerous and debilitating and therefore achieving adequate seizure control with adjunctive AEDs can potentially improve quality of life and reduce accidents requiring emergency and/or routine care. The GDG considered the results of one cost-effectiveness analysis, wherein topiramate and rufinamide were less costly and more effective than standard treatment in the reduction of all seizure types, including 'drop attacks'. However, another cost-utility analysis indicated that topiramate was more costly and less effective than lamotrigine and that rufinamide, while more effective than lamotrigine, was highly unlikely to be cost-effective. These analyses had some serious limitations, but the GDG considered that with the estimated daily cost of rufinamide nearly 10 times that of lamotrigine, it is highly unlikely that the extra benefit observed with rufinamide compared to lamotrigine justifies the substantial additional cost. Therefore, the GDG decided that topiramate and rufinamide should be reserved for those patients for whom standard monotherapy and

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	adjunctive lamotrigine have been ineffective or not tolerated.
Quality of evidence	Evidence was extrapolated from the Lennox-Gastaut syndrome evidence review. The evidence for both topiramate and rufinamide was of low quality. There were no head-to-head comparisons of rufinamide and topiramate with any other antiepileptic drug in Lennox Gastaut syndrome.
Other considerations	Clinical experience with rufinamide is considerably less than with lamotrigine which was shown to be effective.

Recommendation	***108.*** **Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefit and harms	Clinical practice suggests that seizures can be aggravated by these medications. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however their potential to aggravate seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG expertise.
Other considerations	There is no evidence of benefit on use of these medications

10.9 Infantile Spasms (West syndrome)

10.9.1 Introduction

Infantile spasms are a specific seizure type presenting in the first year of life, most commonly between 3 and 9 months of age. Spasms are brief axial movements lasting 0.2-2 seconds, most commonly flexor in nature, involving flexion of the trunk with extension of the upper and lower limbs. They typically occur in clusters, and most commonly on awakening. The EEG characteristically shows random high voltage slow waves and spikes, so called hypsarrhythmia, and together with the developmental plateau typically seen at the onset of spasms, form the triad of 'West' syndrome. However full EEG criteria of hypsarrhythmia are not always seen with spasms, especially at the onset, and in these circumstances management should be the same. Spasms may be seen with many underlying causes, whether genetic (e.g. mutation on CDKL5 gene), structural/metabolic (e.g. tuberous sclerosis) or unknown.

Long term prognosis is poor for neurodevelopmental progress, impaired in 85% of patients. Many respond to first-line therapy; long term neurodevelopmental progress is thought to be better if there is a short lag to treatment, as well as a prompt response to treatment, although the underlying cause is equally relevant. However, 60% will subsequently develop later epilepsy even if spasms initially respond to treatment.

10.9.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with infantile spasms with or without tuberous sclerosis as a cause. The outcomes were the same as other reviews except instead of the proportion of participants achieving seizure freedom we looked at the proportion of participants experiencing a cessation of spasms and the proportion of participants experiencing a resolution of hypsarrhythmia.

10.9.3 Matrix of the evidence for adjunctive therapy

We searched for RCTs comparing the effectiveness of different pharmacological interventions for infantile spasms. The interventions we included in our search were nitrazepam, pyridoxine, adrenocorticotropic hormone, hydrocortisone, prednisolone, prednisone, vigabatrin, topiramate, clobazam, clonazepam, zonisamide and sodium valproate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo							
Nitrazepam							
Prednisolone		1[299]					
Prednisone			2[300,301]				
Hydrocortisone		1[302]					
Vigabatrin	1[303]		4[299,304-				

			[306]					
ACTH				1[299]			1[307]	
	PCB	VGB	ACTH	PNL	PNE	HYD	NPM	

PCB – placebo VGB – vigabatrin ACTH – adrenocortiocotrophic hormone
PNL – prednisolone PNE – prednisone HYD - hydrocortisone
NPM - nitrazepam

10.9.3.1 Vigabatrin versus placebo (in a population without tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin and placebo for cessation of spasms in a population without tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and placebo for resolution of hypsarrhythmia in a population without tuberous sclerosis. (MODERATE QUALITY)

No significant difference between vigabatrin and placebo for at least 70% reduction in seizure frequency in a population without tuberous sclerosis. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and placebo in a population without tuberous sclerosis for the incidence of the following adverse events:

- drowsiness (LOW QUALITY)
- irritability (LOW QUALTY)
- death (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin to placebo was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.9.3.2 Vigabatrin versus ACTH (in a population with tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin and ACTH for cessation of spasms in a population with tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and ACTH for resolution of hypsarrhythmia in a population with tuberous sclerosis. (LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on ACTH than vigabatrin in a population with tuberous sclerosis had an incidence of:

- irritability (MODERATE QUALITY)
- hypertension (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and ACTH for withdrawal due to adverse events in a population with tuberous sclerosis (VERY LOW QUALITY)

No significant difference between vigabatrin and ACTH in a population with tuberous sclerosis for incidence of death. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin to ACTH was identified in a population with tuberous sclerosis experiencing infantile spasms.

10.9.3.3 Vigabatrin versus ACTH (in a population without tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on ACTH compared to vigabatrin had cessation of spasms in a population without tuberous sclerosis although there is uncertainty in the magnitude of clinical effect. (LOW QUALITY)

Significantly more participants on ACTH compared to vigabatrin had resolution of hypsarrhythmia in a population without tuberous sclerosis. (MODERATE QUALITY)

Adverse events – statistically significant results

Significantly more participants on ACTH than vigabatrin in a population without tuberous sclerosis had an incidence of irritability (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and ACTH for withdrawal due to adverse events in a population without tuberous sclerosis. (LOW QUALITY)

No significant difference between vigabatrin and ACTH in a population without tuberous sclerosis for the incidence of the following adverse events:

- gastrointestinal disturbances (LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- increased appetite (LOW QUALITY)
- dermatological problems (LOW QUALITY).

Cost-effectiveness

No economic evidence comparing vigabatrin to ACTH was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.9.3.4 Vigabatrin versus hydrocortisone (in a population with only tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on vigabatrin compared to hydrocortisone had cessation of spasms in a population with only tuberous sclerosis. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and hydrocortisone in a population with only tuberous sclerosis for the incidence of the following adverse events:

- drowsiness (VERY LOW QUALITY)
- hyperexcitability/hyperkinesia (VERY LOW QUALITY)
- sleep disorders (VERY LOW QUALITY)
- weight gain (VERY LOW QUALITY)
- abdominal distension (VERY LOW QUALITY)
- hypertension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin to hydrocortisone was identified in a population with only tuberous sclerosis experiencing infantile spasms.

10.9.3.5 Vigabatrin versus prednisolone (in a population without tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between vigabatrin and prednisolone for cessation of spasms in a population without tuberous sclerosis. (VERY LOW QUALITY)

No significant difference between vigabatrin and prednisolone for resolution of hypsarrhythmia in a population without tuberous sclerosis. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants on prednisolone than vigabatrin in a population without tuberous sclerosis had an incidence of irritability (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between vigabatrin and prednisolone for withdrawal due to adverse events in a population without tuberous sclerosis. (VERY LOW QUALITY)

No significant difference between vigabatrin and prednisolone in a population without tuberous sclerosis for the incidence of following adverse events:

- gastrointestinal disturbances (VERY LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- increased appetite (VERY LOW QUALITY)
- fluid and electrolyte (including high b.p) (VERY LOW QUALITY)
- infection (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing vigabatrin to prednisolone was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.9.3.6 ACTH versus prednisone (in a population with tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants on ACTH compared to prednisone in a population with tuberous sclerosis had cessation of spasms. (MODERATE QUALITY)

Significantly more participants on ACTH compared to prednisone in a population with tuberous sclerosis had resolution of hypsarrhythmia. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing ACTH to prednisone was identified in a population with tuberous sclerosis experiencing infantile spasms.

10.9.3.7 ACTH versus prednisone (in a population with tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – non-statistically significant results

No significant difference between ACTH and prednisone for response to treatment (defined as total cessation of spasms and disappearance of hypsarrhythmia) in a population without tuberous sclerosis. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between ACTH and prednisone for incidence of hypertension in a population without tuberous sclerosis (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing ACTH to prednisone was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.9.3.8 Prednisolone versus ACTH (in a population without tuberous sclerosis)

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between prednisolone and ACTH for cessation of spasms in a population without tuberous sclerosis. (VERY LOW QUALITY)

No significant difference between prednisolone and ACTH for resolution of hypsarrhythmia in a population without tuberous sclerosis. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between prednisolone and ACTH for withdrawal due to adverse events in a population without tuberous sclerosis (VERY LOW QUALITY)

No significant difference between prednisolone and ACTH in a population without tuberous sclerosis for the incidence of the following adverse events:

- gastrointestinal disturbances (VERY LOW QUALITY)
- irritability (VERY LOW QUALITY)
- drowsiness (VERY LOW QUALITY)
- increased appetite (VERY LOW QUALITY)
- fluid and electrolyte (including high b.p) (VERY LOW QUALITY)
- blood pressure above 110/80mmHg (VERY LOW QUALITY)
- blood pressure above 120/90mmHg (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing prednisolone to ACTH was identified in a population without tuberous sclerosis experiencing infantile spasms.

10.9.3.9 Nitrazepam versus ACTH

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between nitrazepam and ACTH for at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between nitrazepam and ACTH for withdrawal due to adverse events (VERY LOW QUALITY)

No significant difference between nitrazepam and ACTH for incidence of death. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing nitrazepam to ACTH was identified in a population experiencing infantile spasms.

10.9.4 New recommendations and link to evidence

First-line treatment in infants with infantile spasms

Recommendation	**109. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when an infant presents with infantile spasms. [new 2012]**
Relative values of different outcomes	Reduction in seizures and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Infantile spasms is a rare seizure type which requires input from specialists with expertise in the area. The adverse events profile of individual drugs needs to be evaluated and fully discussed with parents. This was a recommendation based on the GDG expertise as it is thought important that children with infantile spasms should see, or receive advice from, a specialist. Limited evidence suggests early resolution of hypsarrhythmia leads to better prognosis.
Economic considerations	No economic evidence was available to inform recommendations about the treatment of infantile spasms. However, the GDG considered that discussion with, or referral to a tertiary paediatric specialist and early intervention in this group of patients may lead to a better prognosis, preventing long-term cognitive deterioration and associated decrements to health related quality of life.
Quality of evidence	There was no evidence sought for this recommendation. The recommendation was based on GDG expertise.
Other considerations	The adverse events profile of individual medicines needs to be evaluated and fully discussed with parents. The risk of visual field constriction caused by vigabatrin is unknown with short-term use; the short-term side effects of high dose steroids including high blood pressure, glucose intolerance and immuno-suppression require monitoring.

Recommendation	**110. Offer a steroid (prednisolone or tetracosactide*) or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]**
Relative values of different outcomes	Cessation of spasms, resolution of hypsarrhythmia and side effects are considered important primary outcome measures.
Trade off between clinical benefits and harms	Significantly more participants (without tuberous sclerosis as cause) on ACTH (tetracosactide) than vigabatrin had cessation of spasms and resolution of hypsarrhythmia. No difference was found in efficacy in a study of vigabatrin versus prednisolone or prednisolone versus ACTH or prednisone versus ACTH for those without tuberous sclerosis as cause. The GDG considered the drugs to have clinically relevant differences in their side-effects profile. It is unknown whether short-term use of vigabatrin is associated with the development of visual filed defects. Although visual fields should be monitored, this will be very difficult if not impossible in children with a cognitive age of less than 9 years. Short term side effects of high dose steroids such as high blood pressure and glucose intolerance should be monitored. The evidence indicated that hypertension and irritability are worse with steroids. ACTH had a higher incidence of irritability than vigabatrin whether tuberous sclerosis was the cause or not. Prednisolone had a higher incidence of irritability than vigabatrin in a population where tuberous sclerosis was excluded.
Economic considerations	No economic evidence was available to inform the GDG of the relative cost-effectiveness of any drugs used in the treatment of infantile spasms. The population of children experiencing infantile spasms is quite small, treatment duration is short and it is difficult to weigh up the benefits and harms of treatment in terms of quality of life in children so young. Early diagnosis and treatment are essential as this may impact on longer term cognitive and social outcomes. The potential side-effects of steroids (hypertension, irritability and immuno-suppression leading to potentially severe infections), pose additional costs in terms of management and monitoring.
Quality of evidence	Overall number and quality of studies was limited. There was heterogeneity of cause of infantile spasms, dosage of interventions, and duration of the treatment and follow-up. All of the studies were of limited power and do not exclude the possibility of significant differences between the treatments.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Other considerations	Compared with the original guideline (2004), one additional RCT was appropriate for consideration.

Recommendation	**111. Offer vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide*). Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]**
Relative values of different outcomes	Cessation of spasms, resolution of hypsarrhythmia and adverse events are considered important primary outcome measures.
Trade off between clinical benefits and harms	Vigabatrin is significantly more effective at stopping spasms than steroids in patients with infantile spasms caused by tuberous sclerosis. Significantly more patients (including those with tuberous sclerosis as cause) on ACTH than prednisolone had cessation of spasms and resolution of hypsarrhythmia. There was no significant difference between vigabatrin and ACTH in studies where tuberous sclerosis was the cause. The GDG considered the drugs to have clinically relevant differences in their adverse events profile. It is unknown whether short-term use of vigabatrin is associated with the development of visual filed defects. Although visual fields should be monitored, this will be very difficult if not impossible in children with a cognitive age of less than 9 years. The GDG suggest monitoring of visual fields, where possible. Short term side effects of high dose steroids such as high blood pressure and glucose intolerance should be monitored. The evidence found ACTH had higher incidence of irritability and hypertension than vigabatrin for those with tuberous sclerosis as the cause. The GDG felt that overall the advantages of vigabatrin outweighed the potential adverse effects. Steroids were found to be less effective at stopping seizures but the GDG considered that they are a valuable option if vigabatrin is ineffective.
Economic considerations	No economic evidence was available to inform the GDG of the relative cost-effectiveness of any drugs used in the treatment of infantile spasms associated with tuberous sclerosis. The population of children experiencing infantile spasms is quite small, treatment duration is short and it is difficult to weigh up the benefits and harms of treatment in terms of quality of life in children so young. Early diagnosis and treatment are essential as this may impact on longer term cognitive and social outcomes. The potential side-effects of steroids (hypertension, irritability and immuno-suppression leading to potentially severe infections), pose additional costs in terms of management and monitoring.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Quality of evidence	Overall number and quality of studies was limited. Heterogeneity of cause, dosage of interventions, and duration of the treatment and follow-up. All of the studies were of limited power and do not exclude the possibility of significant differences between the treatments.
Other considerations	No other considerations.

10.9.5 New research recommendations (for full list see section 2.11)

10.9.5.1 Infantile spasms

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

Why this is important

The UK Infantile Spasms Study (UKISS)[bb] demonstrated 14-day outcome efficacy of steroids over vigabatrin, although this excluded children with tuberous sclerosis. This study provided no specific subgroup analysis based on the cause of the spasms. There was no analysis on the effect of treatment lag on the study findings. Further data are available on behavioural outcomes at 14 months and 4 years with regard to different treatments but with no analysis based on cause or treatment lag. Further developmental and cognitive outcomes would be useful, including response by specific cause and by treatment lag.

The research should include:

- prospective randomised design, including subgroup analyses based on both cause and treatment lag; this would require large numbers of patients and would need to be multicentre, possibly involving Western Europe
- EEG outcomes
- developmental status at presentation, and at follow-up
- an attempt to obtain data on pharmaco-resistance.

[bb] Lux AL, Edwards SW, Hancock E et al. (2004) The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 364: 1773–8.

10.10 Dravet syndrome (SMEI)

10.10.1 Introduction

Severe myoclonic epilepsy of infancy, now specifically referred to as Dravet syndrome (as first described by the epileptologist Charlotte Dravet) is an epilepsy syndrome that lies within the GEFS+ (genetic epilepsy with febrile seizures 'plus') spectrum. Typically children will present within the first year of life with prolonged, and often focal febrile seizures, with the subsequent appearance in the second year (or up to four years of life) of other seizure types including focal, generalized tonic-clonic and myoclonic eizures. Development is often normal over the first year, but subsequently over the second year starts to slow. At least 80% of children with this electro-clinical syndrome have a mutation in the sodium channel gene, SCN1A. Although referred to as an 'epileptic encephalopathy', the degree to which the epilepsy contributes to the neuro-developmental impairment is unclear, and there may be a contribution from the genetic background. There are also other individuals who do not develop myoclonus but otherwise fulfill the clinical picture, and therefore are known as severe myoclonic epilepsy borderline (SMEB). The aim of treatment remains to control seizures and minimize the occurrence of status epilepticus where possible. It is important to appreciate that some anti-epileptic medications, particularly lamotrigine may aggravate the seizures, and specifically myoclonic seizures. The long-term prognosis is poor for both seizure control and neuro-developmental outcome and there is an increased mortality, including sudden unexpected death in epilepsy (SUDEP).

10.10.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with Dravet syndrome.

10.10.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for epilepsy in a population with severe myoclonic epilepsy of infancy. The interventions we included in our search were stiripentol, levetiracetam, topiramate, clobazam, clonazepam, phenobarbitaland sodium valproate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo						
Stiripentol	1[308]					
Levetiracetam						
Topiramate						
Clobazam						
Clonazepam						

Phenobarbital								
Sodium valproate								
	Pla	STP	TPM	GLB	CLN	PHB	VPA	LEV

Placebo (Pla) Topiramate (TPM) Stiripentol (STP) Clobazam (CLB)

Levetiracetam (LEV) Sodium valproate (VPA) Phenobarbital (PHB) Clonazepam (CLN)

10.10.4 Adjunctive treatment of Dravet Syndrome (SMEI)

10.10.4.1 Stiripentol adjunctive therapy versus Placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

For people with Dravet syndrome, significantly more patients on stiripentol adjunctive therapy were seizure free compared to placebo; however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

For people with Dravet syndrome, significantly more patients on stiripentol adjunctive therapy experienced at least a 50% reduction in seizure frequency compared to placebo; however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically significant results

For people with Dravet syndrome, significantly more patients on stiripentol adjunctive therapy experienced drowsiness compared to patients taking placebo; however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results

For people with Dravet syndrome, there was no significant difference between stiripentol adjunctive therapy and placebo on the incidence of the following adverse events:

- hyperexcitability (VERY LOW QUALITY)
- aggressiveness (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- loss of appetite (VERY LOW QUALITY)
- loss of weight (VERY LOW QUALITY)
- weight gain (VERY LOW QUALITY)
- neutropenia (1000-1500/Ml) (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events,
- withdrawal due to lack of efficacy,
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

Cost-effectiveness

No economic evidence comparing adjunctive stiripentol to placebo in a population of patients with Dravet syndrome was identified.

10.10.5 New recommendations and link to evidence

First-line treatment in children with Dravet syndrome (SMEI)

Recommendation	**112. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Dravet syndrome. [new 2012]**
Relative values of different outcomes	Reduction in seizures and minimising adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Dravet syndrome is a rare epilepsy syndrome which requires input from specialists with expertise in the area. The adverse events profile of individual drugs needs to be evaluated and fully discussed with parents. This was a recommendation based on the GDG expertise as it is thought important that children with Dravet syndrome should see, or receive advice from, a specialist who has the appropriate experience.
Economic considerations	No economic evidence was available to inform recommendations about the treatment of Dravet syndrome. However, the GDG considered that discussion with, or referral to a tertiary paediatric specialist and appropriate intervention in this group of patients may lead to a better prognosis for seizure control, minimise long-term cognitive deterioration and associated decrements to health related quality of life.
Quality of evidence	There was no evidence sought for this recommendation. The recommendation was based on GDG expertise.
Other considerations	The adverse events profile of individual medicines needs to be evaluated and fully discussed with parents.

Recommendation	**113. Consider sodium valproate or topiramate* as first-line treatment in children with Dravet syndrome. [new 2012]**

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**113. Consider sodium valproate or topiramate* as first-line treatment in children with Dravet syndrome. [new 2012]**
Relative values of different outcomes	Seizure freedom and withdrawal due to adverse events were considered to be the most important outcomes.
Trade off between clinical benefits and harms	No evidence was found for monotherapy treatment of Dravet syndrome (SMEI). On first presentation, the diagnosis of Dravet syndrome may be unclear or uncertain, and therefore treatment choice will be influenced by the predominant seizure type, typically generalised tonic-clonic or myoclonic seizures. Sodium valproate and topiramate have been shown to be effective in the treatment of other generalised seizures and epilepsy syndromes. The drugs recommended above are also likely to reduce the risk of convulsive status epilepticus, in contrast to other drugs including lamotrigine, which may exacerbate myoclonic seizures in this and other epilepsy syndromes (BNF).
Economic considerations	No economic evidence was available to inform the GDG on the cost-effectiveness of any AEDs used in the treatment of children with Dravet syndrome (SMEI). Sodium valproate was shown to be a cost-effective monotherapy in other epilepsy populations and the GDG considered it likely to be cost-effective in this population as well. Based on clinical experience, the GDG considered topiramate to be another effective and possibly cost-effective AED for patients with Dravet syndrome (SMEI).
Quality of evidence	No RCT was found in newly-diagnosed patients which compared sodium valproate or topiramate with another antiepileptic drug. The recommendation was based on GDG consensus opinion and extrapolated evidence from other seizure type and epilepsy syndromes.
Other considerations	No other consideration.

Adjunctive treatment in children, young people and adults with Dravet syndrome (SMEI)

Recommendation	**114. Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 113) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam* or stiripentol as adjunctive treatment. [new 2012]**
Relative values of different outcomes	The GDG considered that the most important outcomes were a greater than 50% reduction in seizures and seizure freedom for this recommendation, as well as a reduction in episodes of convulsive status epilepticus (SE).
Trade off between clinical benefits and harms	Only one study was found which compared stiripentol to placebo as adjunctive treatment to clobazam and sodium valproate and

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**114. Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 113) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam* or stiripentol as adjunctive treatment. [new 2012]**
	this showed a significant difference in favour of stiripentol for seizure freedom and at least a 50% reduction in seizure frequency. The GDG considered the benefits to outweigh the risks of using stiripentol. Patients on stiripentol experience drowsiness and appropriate manipulation of the drug may alleviate this side effect. Caution should be given with any drugs that are metabolised by the liver. Stiripentol impairs the breakdown of VPA and CLB and other AEDs metabolised by the liver.
Economic considerations	No economic evidence was available to inform the GDG on the cost-effectiveness of any AEDs in the treatment of children with Dravet syndrome (SMEI). Stiripentol is a very expensive drug relative to other first line AEDs currently available in the NHS that are used to treat Dravet syndrome (SMEI). The GDG considered that at an average cost of £0.016 per mg, the annual cost of 30 mg per kilogram per day for a 3-year old child of average weight (16.5 kg) is almost £3000. A dose of 30 mg per kilogram is only the average dose of stiripentol and the annual cost would rise with an increased dose and also increased age and weight of the child. The GDG considered that patients with Dravet syndrome (SMEI) where seizures are poorly controlled are at risk of developing convulsive status epilepticus which is associated with an increased risk of mortality and morbidity and hospitalisation. Although the clinical evidence shows adjunctive stiripentol to be more effective than placebo, there is considerable uncertainty as to whether associated health gains, measured in terms of seizure reduction, are worth this substantial extra cost.
Quality of evidence	Low quality evidence. There was only one trial in Dravet syndrome (SMEI), and it included a small number of patients and provided no details of concealment of allocation.
Other considerations	This AED has orphan status. Dravet syndrome (SMEI) is a life-long condition which usually has an onset in the first year of life and is associated with poor seizure control, severe learning difficulties and an increased mortality rate.

Recommendation	**115. Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Withdrawal due to adverse events and incidence of adverse events were considered to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	No other RCTs of AEDs used in Dravet syndrome (SMEI) were identified. Therefore this recommendation is based on the consensus opinion of the GDG. These drugs have the potential to exacerbate seizures in Dravet syndrome (SMEI).
Economic considerations	No economic evidence was available to inform the cost-effectiveness of any AEDs in the treatment of children with Dravet syndrome (SMEI); however the potential for these drugs to aggravate seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use, particularly as these patients are at a higher risk for developing convulsive status epilepticus which is associated with increased risks of hospitalisation, morbidity, and mortality.
Quality of evidence	No RCT evidence was found for any of these AEDs and therefore the recommendation is based on GDG consensus opinion.
Other considerations	The GDG considered that there is no new evidence to challenge drugs to be avoided (from original guideline) but decided to add phenytoin.

10.10.6 New research recommendations (for full list see section 2.11)

10.10.6.1 Epilepsy Syndromes

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

Why is this important

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

Research should include:

- Multicentre randomised controlled comparative trials with centralized national data collection.
- The ketogenic diet as one of the randomised treatments.
- Primary outcome seizure freedom.
- Secondary outcome measures including seizure-reduction, quality of life and cognitive outcome.
- An attempt to obtain some data on pharmaco-resistance.

- The possibility to include all children with specific epilepsy syndromes to be considered for trial.

10.11 Lennox-Gastaut Syndrome

10.11.1 Introduction

Lennox Gastaut syndrome is an epilepsy syndrome characterised by multiple seizure types (including atonic, tonic [often referred to as 'drop attacks'], tonic-clonic and atypical absence seizures), cognitive impairment and specific EEG features. Age of onset is typically between 3 and 10 years, usually before 8 years, with 10-30% having an earlier history of infantile spasms. The characteristic EEG pattern of diffuse slow spike and wave (<2.5Hz) may not be present at onset but may evolve with time; some authors also require the presence of fast (10Hz) rhythms in sleep, with or without tonic seizures, to make the diagnosis. Episodes of non convulsive status epilepticus are common, but may be under recognised. Long term prognosis for both neurocognitive outcome and seizure control is poor, with a high rate of behaviour disorder. Aims of management should be discussed carefully with each family and medication kept to a minimum where possible to avoid toxicity.

10.11.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with Lennox-Gastaut Syndrome.

10.11.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for Lennox-Gastaut syndrome. The following interventions were included in our search; rufinamide, clobazam, clonazepam, felbamate, ethosuximide, lamotrigine, levetiracetam, sodium valproate and topiramate. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo									
Rufinamide	1[309]								
Lamotrigine	2[310,311]								
Topiramate	1[312]								
Levetiracetam									
Felbamate	1[313]								
Ethosuximide									
Clobazam									
Clonazepam									

Sodium valproate										
	Pla	RFM	LTG	TPM	LEV	FBM	ETX	CLB	CLZ	VPA

Placebo (Pla) Rufinamide (RFM) Lamotrigine (LTG) Clonazepam (CLZ)

Topiramate (TPM) Levetiracetam (LEV) Felbamate (FBM) Ethosuximide (ETX)

Sodium valproate (VPA) Clobazam (CLB)

10.11.4 Adjunctive treatment for Lennox-Gastaut syndrome

10.11.4.1 Lamotrigine versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

One economic evaluation [314] of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.11.5.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking lamotrigine adjunctive experienced at least 50% reduction in drop attack seizure frequency compared to placebo. (MODERATE QUALITY)

Significantly more participants taking lamotrigine adjunctive experienced at least 50% reduction in tonic-clonic seizure frequency compared to placebo. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine adjunctive and placebo for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between lamotrigine adjunctive and placebo for the proportion of participants experienced at least 50% reduction in seizure frequency (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking placebo experienced fatigue compared to lamotrigine adjunctive. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine adjunctive and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between lamotrigine adjunctive and placebo for the incidence of the following adverse events:

- pharyngitis (VERY LOW QUALITY)

- fever (VERY LOW QUALITY)
- more intense seizures (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that adjunctive lamotrigine is less costly and more effective than placebo in the treatment of total seizures and drop attack seizures in people with Lennox-Gastaut syndrome. This evidence is partially applicable and has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

10.11.4.2 Topiramate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

One economic evaluation [314] of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.11.5.

Evidence statements

Efficacy – statistically significant results

Significantly more participants taking topiramate adjunctive therapy experienced at least 50% reduction in frequency of all major seizures compared to placebo, however there is uncertainty over the magnitude of this clinical effect. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between topiramate adjunctive therapy and placebo for the proportion of participants free from drop attack seizures. (VERY LOW QUALITY)

No significant difference between topiramate adjunctive therapy and placebo for the proportion of participants experienced at least 50% reduction in drop attack seizure frequency (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking topiramate adjunctive therapy experienced somnolence compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly more participants taking topiramate adjunctive therapy experienced anorexia compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly more participants taking topiramate adjunctive therapy experienced fatigue compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference was found between topiramate adjunctive and placebo for the incidence of the following adverse events:

- nervousness (VERY LOW QUALITY)
- behavioural problems (VERY LOW QUALITY)
- more intense seizures (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that adjunctive topiramate is less costly and more effective than placebo in the treatment of drop attack seizures in people with Lennox-Gastaut syndrome. Adjunctive topiramate is more costly and more effective than placebo in terms of total seizure reduction, with an incremental cost-effectiveness ratio of £58 per additional 1% of successfully treated patients. This evidence is partially applicable and has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.11.4.3 Felbamate versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between felbamate adjunctive therapy and placebo for the proportion of participants free from seizures (atonic and tonic-clonic seizure). (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking felbamate adjunctive therapy experienced anorexia compared to placebo. (MODERATE QUALITY)

Significantly more participants taking felbamate adjunctive therapy experienced vomiting compared to placebo. (MODERATE QUALITY)

Significantly more participants taking felbamate adjunctive therapy experienced somnolence compared to placebo, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Significantly fewer participants taking felbamate adjunctive therapy experienced diarrhoea compared to placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between felbamate adjunctive therapy and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between felbamate adjunctive and placebo for the incidence of the following adverse events:

- upper respiratory tract infection (VERY LOW QUALITY)
- injury (VERY LOW QUALITY)
- fever (VERY LOW QUALITY)
- insomnia (VERY LOW QUALITY)
- nervousness (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- purpura (VERY LOW QUALITY)
- abnormal gait (VERY LOW QUALITY)
- rhinitis (VERY LOW QUALITY)
- ataxia (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing felbamate adjunctive therapy to placebo was identified in a population with Lennox-Gastaut syndrome.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.11.4.4 Rufinamide versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

One economic evaluation [314] of AEDs, including lamotrigine and placebo, used as adjunctive therapy in the treatment of children with Lennox-Gastaut syndrome was identified in the economic literature search. The complete results of this study are presented in section 10.11.4.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in rufinamide adjunctive experienced at least 50% reduction in seizure frequency compared to placebo. (LOW QUALITY)

Significantly more participants in rufinamide adjunctive experienced at least 50% reduction in frequency of tonic-atonic seizures compared to placebo. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between rufinamide adjunctive and placebo for the proportion of participants withdrawn due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants taking rufinamide adjunctive experienced vomiting compared to placebo. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between rufinamide adjunctive and placebo for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

No significant difference was found between rufinamide adjunctive and placebo for the incidence of the following adverse events:

- somnolence (VERY LOW QUALITY)
- pyrexia (VERY LOW QUALITY)
- diarrhoea (VERY LOW QUALITY)

Cost-effectiveness

One economic evaluation based on a decision analytic model showed that adjunctive rufinamide is less costly and more effective than placebo in the treatment of drop attack seizures in people with Lennox-Gastaut syndrome. Adjunctive rufinamide is more costly and more effective than placebo in terms of total seizure reduction, with an incremental cost-effectiveness ratio of £85 per additional 1% of successfully treated patients. This evidence is partially applicable and has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- time to first seizure,
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes

- quality of life outcomes.

10.11.5 Health economic evidence of AEDs used as adjunctive therapy for children with Lennox-Gastaut syndrome

Two studies[314,315] assessing the cost-effectiveness of AEDs used as adjunctive therapy in children with Lennox-Gastaut syndrome were identified in the economic literature search and included in the economic evidence review. See appendix M for full study details.

One study [314] was excluded because it measured outcomes in terms of additional cost per 1% increase in successfully treated patient and was therefore only partially applicable. The other study [315] was included in the economic evidence review.

Economic study characteristics

Table 21: Adjunctive therapy for children with Lennox-Gastaut syndrome - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Verdian (2010)[315]	Potentially serious limitations (a, b, c)	Partially applicable (d)	Decision analytic model; comparators included monotherapy (placebo), lamotrigine, rufinamide and topiramate; time horizon 3 years; clinical data based on indirect treatment comparison of data presented in clinical review[309,311,312]
Benedict (2010) [314]	Potentially serious limitations (a, b)	Partially applicable (e, f)	Decision analytic model; comparators included monotherapy (placebo), lamotrigine, rufinamide and topiramate; time horizon 3 years; clinical data based on indirect treatment comparison of data presented in clinical review[309], [311], [312]; 2 analyses conducted: one on reduction in 'drop attack' seizure frequency and other on percent reduction in total seizure frequency

(a) Authors do not detail how non-reported outcomes for lamotrigine and topiramate were handled. Details of how adverse events were costed were not reported.
(b) Potential conflict of interest in terms of funding source
(c) Estimates of resource use based on 'expert' opinion of five physicians
(d) HRQoL data was not elicited directly from patients and/or carers
(e) Analysis based percent of successfully treated patients, not QALYs
(f) Costs discounted at 3.5% per annum; no discounting applied to estimate of effect

Economic study results

Table 22: Adjunctive therapy for children with Lennox-Gastaut syndrome – Results of Verdian 2010[315]

AED	Total cost (£) per patient	Total effects (QALY)	ICER (£ / QALY)	Uncertainty
LTG	£21,783	1.42		At threshold of £20K and £30K per QALY, probability of LTG being more cost-effective than RUF is 92% and 85% respectively
TPM	£23,360	1.36	Dominated by LTG	At threshold of £20K and £30K per QALY, probability of TPM being more cost-effective than RUF is 48% and 35% respectively (a)
RUF	£24,992	1.44	£154,831 compared to LTG	At threshold of £20K and £30K per QALY, probability of RUF being more cost-effective than LTG is 8% and 15% respectively. At threshold of £20K and £30K per QALY, probability of RUF being more cost-effective than TPM is 52% and 65% respectively. ICER of RUF most sensitive to changes in initial probabilities of response at 3-months.

(a) Presentation of probabilistic sensitivity analysis incomplete in that it only presents comparisons of RUF vs LTG and RUF vs TPM but fails to present comparison of TPM vs LTG.

Table 23: Adjunctive therapy for children with Lennox-Gastaut syndrome – Results of Benedict 2010

AED	Total cost (£) per patient	Total effects (% successfully treated patients)	ICER (£ / 1% increase in successfully treated patients)	Uncertainty
Measured on outcome of reduction in 'drop attack' seizures				
TPM	£50,728	7.2%		At threshold of £100 per 1% increase in successfully treated patients ('drop attacks'), probability of TPM being optimal is 36%
LTG	£50,975	5.2%	Dominated	At threshold of £100 per 1% increase in successfully treated patients ('drop attacks'), probability of LTG being optimal is 10%
RUF	£50,985	11.3%	£62	At threshold of £100 for 1% increase in successfully treated patients, probability of RUF being optimal is 54%; One-way sensitivity analysis indicates ICER for RUF is sensitive to decrease in rate of hospitalisation for 'drop attack' seizures
Monotherapy (placebo)	£51,437	3.3%	Dominated	At threshold of £100 for 1% increase in successfully treated patients, probability of RUF being optimal is 0%
Measured on outcome of reduction in total seizures				
LTG	£37,064	6.9%		Could not be determined from graph (a)
Monotherapy (placebo)	£38,366	2.3%	Dominated	Could not be determined from graph
TPM	£38,557	5.6%	Dominated	Could not be determined from graph

AED	Total cost (£) per patient	Total effects (% successfully treated patients)	ICER (£ / 1% increase in successfully treated patients)	Uncertainty
RUF	£38,828	7.7%	£2,151	Could not be determined from graph (a); One-way sensitivity analysis indicates ICER for RUF is sensitive to decrease in rate of hospitalisation for 'drop attack' seizures

(a) Text states that at threshold of £900 per 1% increase in successfully treated patients RUF has a >80% probability of being optimal; however, the CEAC presented cannot be interpreted to confirm this.

Evidence statements

Two economic evaluations based on decision analytic models show that lamotrigine is likely to be the most cost-effective AED for the adjunctive treatment of children with Lennox-Gastaut syndrome. Lamotrigine was less costly and more effective than topiramate as measured in terms of proportion successfully treated for all seizure types and QALYs gained.

Two studies showed that adjunctive rufinamide is more costly and more effective than lamotrigine and topiramate, but neither study demonstrates it to be the most cost-effective. Cost-effectiveness was indeterminable in one analysis as the measurement of effect was not QALYs and the ICER was very sensitive to assumptions about the rate of hospitalisation caused by 'drop attack' seizures. In the other analysis, rufinamide had an unacceptably high ICER compared to lamotrigine (£154,831). Both studies are partially applicable and have potentially serious limitations.

10.11.6 New recommendations and link to evidence

Recommendation	**116. Discuss with, or refer to, a tertiary paediatric epilepsy specialist when a child presents with suspected Lennox–Gastaut syndrome. [new 2012]**
Relative values of different outcomes	Reduction in seizures and minimising adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Lennox-Gastaut syndrome is a rare epilepsy syndrome which requires input from specialists with expertise in the area. The adverse events profile of individual drugs needs to be evaluated and fully discussed with parents. This was a recommendation based on the GDG expertise as it is thought important that children with Lennox-Gastaut should see, or receive advice from, a specialist who has the appropriate experience.
Economic considerations	Eeconomic evidence relating to the treatment of Lennox-Gastaut syndrome was isolated to drug options for use as adjunctive therapy. The GDG considered that discussion with, or referral to a tertiary paediatric specialist and appropriate intervention in this group of patients may lead to a better prognosis for seizure control, minimise long-term cognitive deterioration and associated decrements to health related quality of life.
Quality of evidence	There was no evidence sought for this recommendation. The recommendation was based on GDG expertise.
Other considerations	The adverse events profile of individual medicines needs to be evaluated and fully discussed with parents.

First-line treatment in children with Lennox-Gastaut syndrome

Recommendation	**117. Offer sodium valproate as first-line treatment to children with Lennox–Gastaut syndrome. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.
Trade off between clinical benefits and harms	The potential benefits of reducing seizures need to be balanced against the potential for adverse effects. No RCT evidence was retrieved on sodium valproate in this area. There is however evidence that sodium valproate is effective in reducing seizures in idiopathic generalised epilepsy and the GDG opinion was that this evidence could be extrapolated to children and young people with Lennox-Gastaut syndrome.
Economic considerations	No economic evidence was available to determine the cost-effectiveness of any AEDs used as first-line treatment in a population of patients with newly diagnosed Lennox-Gastaut syndrome. However, the GDG considered that at initial presentation, treatment choice is influenced by the predominant seizure type, and in this case that is typically a generalised seizure type. Therefore, the GDG extrapolated the evidence of cost-effectiveness for sodium valproate from the results of SANAD, presented in section 10.3.8.
Quality of evidence	We found no RCTs in newly diagnosed patients or that compared sodium valproate with another antiepileptic drug. We also found no RCTs that compared two drugs as add-on treatment. The recommendation is based on extrapolated evidence from idiopathic generalised epilepsy and GDG consensus opinion.
Other considerations	The GDG considered that there is no new evidence to challenge first-line treatment (from original guideline). At initial presentation, the diagnosis of the syndrome may be unclear or uncertain, and therefore treatment choice will be influenced by the predominant seizure type. Low rates of seizure freedom can be expected in this syndrome as verified by results of clinical trials. Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose.

Adjunctive treatment in children, young people and adults with Lennox-Gastaut syndrome

Recommendation	**118. Offer lamotrigine as adjunctive treatment to children, young people and adults with Lennox–Gastaut syndrome if first-line treatment with sodium valproate is ineffective or not tolerated. [new 2012]**
Relative values of different outcomes	Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Lamotrigine adjunctive treatment is more effective in reducing at least 50% the seizure frequency and has a similar side effects profile when compared to placebo.
Economic considerations	The treatment of Lennox-Gastaut syndrome generally requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. The GDG considered the results of two cost-effectiveness analyses, wherein lamotrigine was less costly and more effective than standard monotherapy in terms of reducing the frequency of all seizures and 'drop attacks' and less costly and more effective than topiramate in reducing the frequency of all seizure types and produced more QALYs. The analyses had some potentially serious limitations, but the GDG considered that lamotrigine is a relatively inexpensive AED and was shown to be effective in terms of reducing the number of 'drop attacks' and tonic-clonic seizures in the clinical review. It was also associated with fewer side effects than topiramate and rufinamide. On this basis, the GDG judged it the AED most likely to be considered cost-effective.
Quality of evidence	The two studies included for the comparison of lamotrigine adjunctive versus placebo were of low quality due to serious limitations in the study design as both of them had no information on randomisation and no allocation concealment.
Other considerations	Sodium valproate inhibits metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose.

Recommendation	**119. Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 118) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. [new 2012]**
Relative values of different outcomes	Seizure freedom, at least 50% reduction in seizure frequency and withdrawal due to adverse events were considered to be the most important outcomes.
Trade off between clinical benefits and harms	If adjunctive treatment is not tolerated or ineffective further treatment may be successful but the GDG felt that this should be discussed with a tertiary epilepsy specialist. The balance between reducing seizures (which may be debilitating) and adverse effects needs to be considered when choosing drug treatment. Rufinamide adjunctive treatment was more effective in reducing at least 50% the seizure frequency. Both rufinamide and topiramate treatments had worst side-effect profile compared to placebo.
Economic considerations	The treatment of Lennox-Gastaut syndrome generally requires a number of concomitant AEDs because no single AED is likely to bring about a satisfactory response. 'Drop-attacks', common in people with Lennox-Gastaut can be debilitating and dangerous, therefore achieving adequate seizure control with adjunctive AEDs can potentially improve quality of life and reduce accidents requiring emergency and/or routine care. The GDG considered the results of one cost-effectiveness analysis, wherein topiramate and rufinamide were less costly and more effective than standard treatment in the reduction of all seizure types, including 'drop attacks'. But another cost-utility analysis indicated that topiramate was more costly and less effective than lamotrigine and that rufinamide, while more effective than lamotrigine was highly unlikely to be cost-effective. The analyses had some serious limitations, but the GDG considered that with the estimated daily cost of rufinamide nearly 10 times that of lamotrigine, it is highly unlikely that the extra benefit observed with rufinamide compared to lamotrigine justifies the substantial additional cost. Therefore, the GDG decided that topiramate and rufinamide should be reserved for those patients for whom standard monotherapy and adjunctive lamotrigine have been ineffective or not tolerated.
Quality of evidence	The evidence for both topiramate and rufinamide was of low quality. There were no head-to-head comparisons of rufinamide and topiramate with any other antiepileptic drug in Lennox Gastaut Syndrome.
Other considerations	Clinical experience with rufinamide is considerably less than with lamotrigine which was shown to be effective.

Recommendation	**120. Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefit and harms	Clinical practice suggests that seizures can be aggravated by these medications, and can compromise cognition with risk of non-convulsive status epilepticus. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however their potential to aggravate seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG expertise.
Other considerations	There is no evidence of benefit on use of these medications

Recommendation	**121. Only offer felbamate* in centres providing tertiary epilepsy specialist care and when treatment with all of the AEDs listed in recommendations 119 and 120 has proved ineffective or not tolerated. [new 2012]**
Relative values of different outcomes	Reduction in seizures and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefit and harms	Felbamate adjunctive was not found to be more effective compared to placebo and demonstrated a serious side-effect burden.
Economic considerations	No economic evidence is available to evaluate the relative cost-effectiveness of felbamate in the treatment of people with Lennox-Gastaut syndrome. However, the potential for serious adverse events, such as aplastic anaemia, and the need for ongoing monitoring make it unlikely to be a cost-effective AED for the average patient.
Quality of evidence	One RCT was identified which had serious limitations.
Other considerations	The GDG considered felbamate to be a last-line therapy, reserved for patients who have not responded to alternative, cost-effective treatment options. It is only available on a named patient basis. Use of felbamate must be accompanied by monitoring of liver and bone marrow function.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

10.12 Benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome and late- onset childhood occipital epilepsy (Gastaut type)

10.12.1 Introduction

Benign epilepsy with centrotemporal spikes (formerly benign rolandic epilepsy) is one of the most common epilepsies in childhood. It is characterised by focal motor seizures, in the majority from sleep, in an otherwise normal individual. The EEG characteristically shows focal spikes in the centrotemporoal regions, unilateral or bilateral, enhanced by sleep. The majority of children present between 5 and 8 years, with all seizures resolving by the age of 14 years. Seizure frequency is highly variable; in some seizures will be infrequent. At onset therefore, there may be some discussion as to whether treatment is necessary, remembering the term benign refers to the prognosis rather than the seizures themselves. Some families prefer to avoid treatment if possible. Some authors have reported associated verbal deficits on detailed testing at the time of the active epilepsy; whether treatment impacts on the occurrence of this is unknown.

Panayiotopoulos syndrome is an epilepsy of early onset, mean 5 years of age (range 1-14) characterised by infrequent seizures, commonly prolonged. Seizures begin with autonomic features such as vomiting, pallor and sweating followed by eye deviation and impairment of consciousness. Status epilepticus may occur. Prognosis is excellent, many individuals may haveone or two seizures only, and so treatment is often unnecessary. Initially described as an occipital epilepsy, there is evidence that regions outwith the occipital lobe generate the seizures and therefore it is now more accurately referred to as an autonomic epilepsy. EEG may demonstrate occipital spikes, although multifocal spikes are also often seen.

Late onset childhood occipital epilepsy (Gastaut type) is an epilepsy that presents later, at a mean age of 8 years (range 3-16). Seizures are characterised by initial visual hallucinations (than often can be drawn in detail) and/or ictal blindness and illusions. Seizures are frequent, brief and diurnal; impairment of consciousness is rare unless associated with hemi-clonic or generalised convulsions. Postictal headache is common. The EEG is characterised by occipital spikes which attenuate on eye opening (fixation off sensitivity). Seizures often remit within 2-5 years.

10.12.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with BECTS, Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type).

10.12.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for epilepsy in a population with benign focal epilepsies of childhood. The interventions we included in our search were lamotrigine, levetiracetam, topiramate, gabapentin, oxcarbazepine, sulthiame, sodium valproate and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found, in this case, no section on this comparison is included in the chapter.

Placebo									
Lamotrigine									
Levetiracetam									
Topiramate									
Gabapentin									
Oxcarbazepine					1[316]				
Sulthiame	1[317]								
Sodium valproate									
Carbamazepine						1[318]			
	PLA	CBZ	VPA	GBP	LEV	TPM	OXC	SL M	LTG

PLA - Placebo LTG - Lamotrigine LEV - Levetiracetam

TPM - Topiramate GBP - Gabapentin OXC - Oxcarbazepine

SLM - Sulthiame VPA - Sodium valproate CBZ - Carbamazepine

10.12.4 Monotherapy for the treatment of adults and children with BECTS, Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type)

10.12.4.1 Sulthiame versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more patients taking sulthiame monotherapy were seizure free compared to placebo. (HIGH QUALITY)

Efficacy – statistically non-significant results

No significant difference between sulthiame monotherapy and placebo for withdrawal due to adverse events. (HIGH QUALITY)

Adverse events – statistically non-significant results

No significant difference between sulthiame monotherapy and placebo for withdrawal due to lack of efficacy. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sulthiame monotherapy to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes

10.12.4.2 Levetiracetam versus oxcarbazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search. Levetiracetam monotherapy and oxcarbazepine monotherapy were compared as part of the NCGC economic model evaluating different monotherapy AEDs used in the treatment of adults with newly diagnosed focal epilepsy. For a description and results of the analysis, see section 10.3.6. No similar comparison was available for the economic model built to evaluate AEDs for children with newly diagnosed focal epilepsy.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for seizure freedom. (VERY LOW QUALITY)

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)

There was no significant difference between levetiracetam monotherapy and oxcarbazepine monotherapy for the incidence of decreased appetite. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing levetiracetam monotherapy to oxcarbazepine monotherapy was identified in a population of patients with BECTS. In an adult population with newly diagnosed focal epilepsy oxcarbazepine monotherapy was less costly and more effective than levetiracetam monotherapy. This analysis has minor limitations and is partially applicable to this review.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.12.4.3 Topiramate versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search. Topiramate monotherapy and carbamazepine monotherapy were compared as part of the NCGC economic model evaluating different monotherapy AEDs used in the treatment of adults with newly diagnosed focal epilepsy. For a description and results of the analysis, see section 10.3.6. No similar comparison was available for the economic model built to evaluate AEDs for children with newly diagnosed focal epilepsy.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for seizure freedom (VERY LOW QUALITY)

Adverse events - statistically significant results

Significantly more participants in the carbamazepine monotherapy group had an incidence of rash compared to participants in the topiramate monotherapy group. (LOW QUALITY)

Adverse events - statistically non- significant results

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for withdrawal due to adverse events (VERY LOW QUALITY).

There was no significant difference between topiramate monotherapy and carbamazepine monotherapy for the incidence of somnolence (VERY LOW QUALITY).

Cost-effectiveness

No studies comparing topiramate monotherapy to carbamazepine monotherapy were identified. In an adult population with newly diagnosed focal epilepsy carbamazepine monotherapy was less costly and more effective than topiramate monotherapy. This analysis has minor limitations and is partially applicable to this review.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- time to first seizure

- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes

10.12.5 New recommendations and link to evidence

First- line treatment in children and young people with BECTs, Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type)

Recommendation	**122. Discuss with the child or young person, and their family and/or carers, whether AED treatment for benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) is indicated. [new 2012]**
Relative values of different outcomes	Seizure freedom and reduction in seizure frequency are important outcomes, but so too is the avoidance of adverse effects of drug treatment.
Trade off between clinical benefits and harms	No RCT evidence was found for Panayiotopoulos syndrome or late onset childhood occipital epilepsy. For BECTS we found evidence that sulthiame was more effective than placebo, however this drug is unlicensed in the UK. In one unblinded and one single-blinded study there were no differences found in efficacy or tolerability between levetiracetam and oxcarbazepine or carbamazepine compared to topiramate (apart from a significantly higher rate of rash with carbamazepine). Due to the limited evidence the GDG decided to extrapolate the results for BECTS , Panayiotopoulos syndrome or late onset childhood occipital epilepsy from the focal seizures review because they are epilepsies characterised by focal seizures. This recommendation was based on GDG consensus. The balance between treating BECTs and the adverse effects of drug treatment should be evaluated in conjunction with family and/or carer to determine whether the child requires treatment. In some cases, seizures are so infrequent that the child and their family and/or carers may decide to forgo treatment in order to avoid the possible side effects.
Economic considerations	No economic evidence in this population was available; however, the decision as to whether treatment is indicated or not should be made very carefully as the possible cost and quality of life consequences could be substantial if a patient's seizures are poorly controlled. If seizures were poorly controlled, the cost savings generated by opting against drug treatment could be quickly offset by hospital admissions, outpatient appointments and/or GP consultations.

Recommendation	**122. Discuss with the child or young person, and their family and/or carers, whether AED treatment for benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) is indicated. [new 2012]**
Quality of evidence	The quality of evidence ranged from high to very low depending on outcome and there was no evidence comparing drug treatment to no treatment apart from sulthiame against placebo but this is unlicensed in the UK. This recommendation was based on GDG consensus opinion.
Other considerations	No other considerations.

Recommendation	**123. Offer carbamazepine♣ or lamotrigine♣ as first-line treatment to children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type). [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure freedom, withdrawal due to adverse events and time to treatment failure, time to first seizure and time to 12 month remission were the most clinically important outcomes for this recommendation.
Trade off between clinical benefits and harms	We found evidence that sulthiame was more effective than placebo, however this drug is unlicensed in the UK. There were no differences in seizure freedom, withdrawal due to lack of efficacy, withdrawal due to adverse events or incidence of adverse events between levetiracetam and oxcarbazepine and carbamazepine compared to topiramate, apart from carbamazepine had significantly higher rates of rash than topiramate. Due to the limited evidence (two studies unblinded and single blinded) the GDG decided to extrapolate the results for BECTS, Panyaiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type) from the focal seizures review because epilepsies characterised by focal seizures. The extrapolated results from focal seizures found lamotrigine and carbamazepine both had efficacy. Carbamazepine had a longer time to first seizure (in the meta-analysis of direct evidence and the IPD results) and there was no significant difference for seizure freedom. Lamotrigine has a better adverse events profile than carbamazepine. Lamotrigine requires slow titration to reduce risk of rash, which may make it unsuitable for individuals requiring rapid control. The meta-analysis of direct evidence found significantly more participants on carbamazepine compared to lamotrigine withdrew due to adverse events and the direct evidence and IPD results showed carbamazepine prolonged the time to first seizure and had a shorter time to withdrawal than

♣ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	lamotrigine. Oxcarbazepine has a similar adverse events profile and efficacy to carbamazepine and lamotrigine, except the IPD analysis found that oxcarbazepine had longer time to first seizure than oxcarbazepine. Whereas the direct evidence found no difference. Carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations. Carbamazepine had more efficacy than sodium valproate but sodium valproate showed no significant differences to oxcarbazepine. Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity. In children, lamotrigine and carbamazepine have similar efficacy and adverse events profiles, with the exception of incidence of dizziness which is more prominent with carbamazepine. Lamotrigine and oxcarbazepine had more efficacy (IPD results for time to withdrawal, but no difference in the direct evidence) and less adverse events than phenytoin. It should be noted that the IPD meta-analysis for lamotrigine versus phenytoin was based on indirect evidence. Phenytoin had no significant difference when compared to carbamazepine. Topiramate had similar efficacy to sodium valproate and oxcarbazepine. However phenytoin and topiramate have disadvantages due to drug interactions and their adverse events profiles. Gabapentin was less effective than other AEDs. Vigabatrin is not recommended because of its adverse effects in long-term use. Phenobarbital is not recommended because of adverse effects. Clobazam is not recommended because of concerns with tolerability. Therefore these drugs were not thought to be appropriate to recommend as first-line treatment.
Economic considerations	Although no economic evidence on the relative cost-effectiveness of AEDs was available for this population specifically, the GDG considered the results of the economic modelling undertaken for the treatment of focal epilepsy to be applicable to this group of patients as well. As children with BECTS, Panyaiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type) are likely to respond to the first AED offered and are likely to experience spontaneous remission during adolescence, these drugs may be even more cost-effective in this group than in the general population of patients with focal epilepsy. Other AEDs licensed for use as monotherapy in focal epilepsy, including gabapentin, levetiracetam and topiramate, were not shown to be cost-effective at current 2011 prices. However, as non-proprietary levetiracetam is expected to come to market within the near future and its relative cost-effectiveness compared with the AEDs listed in this recommendation is sensitive to changes

	in unit cost. Because it is difficult to know not only how much the price of levetiracetam will drop with the introduction of generic competition, but also how much the cost of other AEDs may change as well, the GDG made recommendations for the treatment of children with BECTS , Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type) based on current information. A subsequent recommendation provides additional information to users of the guideline regarding how much the cost of levetiracetam must drop in order to be considered cost-effective and how this might affect its relative placement among first-line AEDs.
Quality of evidence	There was no evidence for Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type) and little evidence available for BECTS. The studies that did exist for BECTs showed no significant differences except for sulthiame, which is not licensed in the UK. The quality of this evidence was mainly very low and there was a lack of blinding and allocation concealment. The sulthiame study was high quality. As we extrapolated the results from focal seizures, the quality is relevant for these studies. In adults, the studies included in the evidence were of low quality due to serious limitations in the study design. Many of the studies were unblinded or had inadequate detailing of randomisation and allocation concealment. With some of the studies having high dropout. One important study (the SANAD trial Marson, 2007 [41]) was a large pragmatic trial which informed many of the comparisons. This was an unblinded multicentre study. In children, three studies were included (Nieto-Barrera, 2001) [164], Guerreiro , 1997 and Zamponi 1999 which the majority were unblinded with limitations.
Other considerations	The GDG considered that BECTs will remit by the age of 14 years and prognosiss for remission is excellent therefore treatment is of short duration. The GDG found no evidence to refute the place of drugs listed as first-line in the original guideline except for topiramate which has been advised as adjunctive therapy. Sodium valproate inhibits metabolism of lamotrigine. This needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be concomitant increase in the lamotrigine dose. Oxcarbazepine and carbamazepine are hepatic enzyme-inducing drugs and may interact with other medications; this may influence the choice of AED in some individuals. Furthermore, the GDG considered the potential for carbamazepine and oxcarbazepine to exacerbate or unmask continuous spikes and waves during slow sleep (CSWS), which occur in some children with BECTS. The metabolism of lamotrigine may be increased by oestrogens in

	in contraceptives. In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration. The GDG considered that different patients react differently to the different drugs and different options may need to be tried with the hope of getting the balance right between seizure freedom and side effects. If the first AED is ineffective, a second AED should be added alongside the initial AED and, if seizures are controlled, the first AED may be withdrawn, recognising that some patients will prefer to remain on two AEDs if seizure-free. The GDG considered that it is generally preferable to avoid polytherapy.

Recommendation	**124. Levetiracetam is not cost effective at June 2011 unit costs[cc]. Offer levetiracetam[*], oxcarbazepine[*], or sodium valproate (provided the acquisition cost of levetiracetam falls to at least 50% of June 2011 value documented in the National Health Service Drug Tariff for England and Wales) if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs. Be aware that carbamazepine and oxcarbazepine may exacerbate or unmask continuous spike and wave during slow sleep, which may occur in some children with benign epilepsy with centrotemporal spikes. Be aware of teratogenic risks of sodium valproate (see recommendation 83).[new 2012]**
Relative values of different outcomes	Seizure freedom, withdrawal due to adverse events and withdrawal due to lack of efficacy were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Although both levetiracetam and carbamazepine-controlled-release had very similar findings in terms of efficacy, levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine-extended release which is why it was not recommended as the drug of first choice. However it may be useful for people when the first line AEDs are contraindicated. The GDG considered that levetiracetam lacks interaction with other drugs.
Economic considerations	Other AEDs licensed for use as monotherapy, including gabapentin, levetiracetam and topiramate, were not shown to be cost-effective at current 2010 prices. Given the current use of levetiracetam in clinical practice and the imminent arrival of a generic product to the market the GDG considered it important to provide additional information to users of the guideline regarding the circumstances under which levetiracetam is likely to be a cost-effective first line AED. The analyses showed that there is quite a bit of uncertainty around the cost-effectiveness of levetiracetam, driven by a limited clinical evidence base and questions about its future cost. Lamotrigine was found to be more cost effective than levetiracetam, and this result was consistent across a range of sensitivity analyses (dominating levetiracetam in some and representing better value for money given the NICE threshold in others). Carbamazepine was also more cost effective than levetiracetam, except when levetiracetam was assumed to be more tolerable than carbamazepine and 70 percent less costly than it is currently.

[cc] Estimated cost of a 1500 mg daily dose was £2.74 at June 2011. Cost taken from the National Health Service Drug Tariff for England and Wales, available at www.ppa.org.uk/ppa/edt_intro.htm

[*] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	The GDG next considered the situation wherein carbamazepine and lamotrigine are considered unsuitable or have been poorly tolerated. Based on the interpretation of the evidence, the GDG recommended that sodium valproate and oxcarbazepine are considered in this group. The sensitivity analysis around cost was undertaken for this clinical scenario as well, and found the probability of levetiracetam being considered cost-effective relative to sodium valproate and oxcarbazepine improves as price decreases. A 50 percent price decrease makes levetiracetam more cost effective than oxcarbazepine but not cost effective compared to sodium valproate. However, if levetiracetam is more tolerable than carbamazepine, then a 50 percent price decrease makes levetiracetam cost-effective compared to both drugs, although substantial uncertainty surrounds this conclusion. When all recommended first-line AEDs (carbamazepine, lamotrigine, oxcarbazepine and sodium valproate) are removed from the analysis due to contraindications, gabapentin is the AED most likely to be considered cost-effective. However, if the future acquisition cost of levetiracetam is 20 to 30 percent less than what it is currently, then levetiracetam becomes the most cost-effective AED given the NICE willingness to pay threshold. The GDG considered this scenario and concluded that in the situation where all recommended first line drugs are contraindicated or unsuitable, there is a likelihood that gabapentin and topiramate might not be appropriate either, thus lending further weight to the choice of levetiracetam even at current costs. With the expectation that a modest drop in its price will move it from marginally not cost-effective to most cost-effective, the GDG decided it should be offered in preference to gabapentin in this clinical situation. The GDG considered the uncertainties around levetiracetam driving the results of the base case and various sensitivity analyses. They also accepted that they did not know not only how much the price of levetiracetam will drop with the introduction of generic competition, nor how much the cost of other AEDs might change as well. After careful consideration, the GDG determined that levetiracetam should be offered as a first-line treatment of children with BECTS, Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type) under the two circumstances. Firstly, in the circumstance when all the recommended first-line treatments (carbamazepine, lamotrigine, oxcarbazepine and sodium valproate) are unsuitable. Secondly, as an alternative to oxcarbazapine and sodium valproate (when carbamazepine and lamotrigine are unsuitable, poorly tolerated or ineffective), if levetiracetam can be acquired for a cost at least 50 percent less than June 2011 unit costs. The GDG felt that this recommendation and the detail include therein, would clearly outline the conditions under which treatment with levetiracetam would represent a cost-effective use of limited NHS resources.
Quality of evidence	There was no evidence found for benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome and late onset

	childhood occipital epilepsy (Gastaut type) so we extrapolated from focal seizures for newly diagnosed epilepsy. One trial with high dropout rates in both arms showed there was no significant difference between levetiracetam and carbamazepine in the proportion of seizure free participants and withdrawal due to adverse events. However, significantly higher proportion of participants on levetiracetam withdrew due to lack of efficacy compared to carbamazepine.
Other considerations	This is a partly GDG consensus opinion based recommendation. Levetiracetam is only licensed for people over 16 years old. It is useful because it does not interact with hormonal contraception. The GDG opinion was that the limited evidence currently available suggests that levetiracetam does not carry an increased risk of teratogenicity.

Recommendation	**125. Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 123 and 124). [new 2012]**
Relative values of different outcomes	In children, young people and adults with these syndromes there should be careful evaluation about the need for treatment. However if treatment required, seizure freedom, withdrawal due to adverse events and time to treatment failure, time to first seizure and time to 12 month remission were the most clinically important outcomes for this recommendation.
Trade off between clinical benefits and harms	We extrapolated the results from focal seizures for this recommendation. Phenytoin had less efficacy and more adverse events than lamotrigine, oxcarbazepine and no significant difference compared to carbamazepine. Topiramate had similar efficacy sodium valproate and oxcarbazepine. However phenytoin and topiramate have disadvantages due to drug interactions and their adverse events profiles. Gabapentin was less effective than other AEDs. Vigabatrin is not recommended because of its adverse effects in long-term use. Phenobarbital is not recommended because of adverse effects. Clobazam is not recommended because of concerns with tolerability. Therefore these drugs were not thought to be appropriate to recommend as first-line treatment. Levetiracetam and carbamazepine controlled-release had very similar findings in terms of efficacy, but levetiracetam had a higher withdrawal rate due to lack of efficacy compared to carbamazepine-controlled-release which is why it was not recommended as the drug of first choice. However the GDG considered it to be useful for people in whom other first line AEDs are not suitable and that levetiracetam lacks interaction with other drugs. The GDG considered that the five AEDs (lamotrigine, carbamazepine, oxcarbazepine, sodium valproate and levetiracetam) offered as first line treatment in newly diagnosed focal seizures may have instances where they are tolerated but are not effective. Therefore due to the concerns with the other AEDs, the GDG agreed that in these cases adjunctive treatment should be considered.
Economic considerations	The original cost-effectiveness analysis undertaken for the guideline indicates that the AEDs used as adjunctive therapy for refractory focal seizures were more effective and more costly than continuing patients on monotherapy. However, adjunctive therapy with a subset of AEDs may be cost-effective at the NICE threshold of £20,000 per QALY. There is considerable uncertainty as to which AED represents the optimal use of NHS resources as much depends on what is appropriate for the individual patient and on his/her previous treatment history.

Quality of evidence	This recommendation was based on the clinical expertise of the GDG and via consensus.
Other considerations	Sodium valproate would not be first choice in females of present or future child-bearing potential, because of increased risks of teratogenicity. Sodium valproate inhibits metabolism of lamotrigine. This needs to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be concomitant increase in the lamotrigine dose. Oxcarbazepine and carbamazepine are hepatic enzyme-inducing drugs and may interact with other medications; this may influence the choice of AED in some individuals. The metabolism of lamotrigine may be increased by oestrogens in contraceptives. In the event of using an alternative drug, rash, hyponatraemia, enzyme induction, CNS related and other adverse events from the previous drugs should all be taken into consideration.

Adjunctive treatment in children and young people with BECTs, Panayiotopoulos syndrome and late onset childhood occipital epilepsy (Gastaut type)

Recommendation	**126. Offer carbamazepine♣, clobazam♣, gabapentin♣, lamotrigine♣, levetiracetam♣, oxcarbazepine ♣, sodium valproate or topiramate♣ as adjunctive treatment to children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) if first-line treatments (see recommendations 123 and 124) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	In children, young people and adults, the achievement of seizure freedom or at least a 50% reduction in seizure frequency were considered to be the most clinically relevant outcomes. Tolerability, as measured by withdrawals due to adverse events, was also considered important.
Trade off between clinical benefits and harms	We extrapolated the results from focal seizures for this recommendation. The evidence for adults showed that significantly more participants receiving clobazam, levetiracetam, levetiracetam extended-release, oxcarbazepine and topiramate achieved seizure freedom than placebo. Significantly more on gabapentin, oxcarbazepine, lamotrigine, levetiracetam and topiramate experienced at least a 50% reduction in seizure frequency when compared to placebo. From the evidence for children, significantly more participants on lamotrigine and oxcarbazepine compared to placebo experienced at least a 50% reduction in seizure frequency. More people on oxcarbazepine (adults and children) achieved seizure freedom than those on placebo in a refractory population on monotherapy. In children, significantly more participants on levetiracetam compared to placebo experienced at least a 50% reduction in seizure frequency. The drugs recommended above had unfavourable adverse events profiles, but the GDG found this unsurprising given that they were being evaluated as combination treatment in a refractory population. Many of the adverse events observed in the trials were dose related and in clinical practice these can be mitigated

♣ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	through careful dose titration. Significantly more participants receiving gabapentin, lamotrigine, topiramate and oxcarbazepine withdrew due to adverse events compared to placebo. Gabapentin had higher incidence of somnolence, dizziness and ataxia and aggravation of seizures when compared to placebo. There was no significant difference between levetiracetam and placebo for withdrawal due to adverse events although incidence of adverse events was significantly higher in the levetiracetam arm. No specific adverse events were reported in the trial for clobazam, but GDG considered its tendency to have sedative side effects and its efficacy can wane over extended use. Oxcarbazepine and lamotrigine had a less favourable adverse events profile compared to placebo. Topiramate had higher incidence of headache when compared with lamotrigine. In children taking lamotrigine the incidence of dizziness, tremor, nausea and ataxia were higher compared to to placebo. A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. For the drugs recommended here, the treatment benefits outweighed the harms for the average patient and the QALYs gained justified the additional costs over placebo (no adjunctive AED).
Economic considerations	We extrapolated from the economic considerations for focal seizures. Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. The original cost-effectiveness analysis undertaken for the guideline indicates that there is considerable uncertainty as to which AED represents the optimal use of NHS resources as a great deal depends on what is appropriate for the individual patient and on his/her previous treatment history. The GDG chose to recommend lamotrigine and oxcarbazepine on the basis that they were the two AEDs with the greatest probability of being cost-effective in the base case and other scenarios. Therefore, if either lamotrigine or oxcarbazepine have not been tried as monotherapy, either first or second-line, then they are likely to represent cost-effective choice s to add-in as adjunctive therapy. The GDG felt that some combinations might be more effective or more tolerable, and thus might be more cost effective, but neither the clinical evidence review nor economic model was designed to identify particular AED combinations. Given that lamotrigine and oxcarbazepine are among AEDs recommended as first-line treatment of newly diagnosed focal seizures, a patient with refractory focal seizures requiring further

	treatment may have already tried one or both. The GDG recommended gabapentin on the basis that in the base case, it was likely to be the most cost-effective AED when lamotrigine and oxcarbazepine were not relevant treatment options. However, given the uncertainty highlighted by the results of the other sensitivity analyses, particularly around the estimates of seizure freedom and assumptions of cost, the GDG decided to recommend topiramate as an additional choice for adjunctive therapy. The GDG considered the results of the base case analysis, in which levetiracetam, although the most effective adjunctive AED, was not shown to be cost-effective given the NICE willingness to pay threshold. It was also unlikely to be considered cost-effective compared to gabapentin and topiramate when lamotrigine and oxcarbazepine were removed from the analysis (assuming they have been already tried as monotherapy). The GDG looked to a series of sensitivity analyses around projected reductions in the price of levetiracetam in order to determine the price point at which the drug might become cost effective. The sensitivity analyses showed that the unit cost of levetiracetam need only come down by 30 percent in order to dominate oxcarbazepine and be considered cost-effective compared to lamotrigine (ICER=£19,264 per QALY). It also becomes the most cost-effective drug under the £20,000 per QALY threshold when lamotrigine and oxcarbazepine are excluded; that is, levetiracetam dominates topiramate (even when only non-proprietary costs are used) and has an ICER of £17,213 compared to gabapentin. The GDG considered the uncertainties around levetiracetam and how its future cost might impact its relative cost effectiveness compared to other available AEDs used in the treatment of refractory focal seizures. They also accepted that they knew neither how much the price of levetiracetam will drop with the introduction of generic competition, nor how much the cost of other AEDs might change as well. The GDG considered the dramatic reduction in the cost of other AEDs, such as lamotrigine and topiramate, following loss of patent protection and introduction of generic competition. Looking to these other examples, they considered it very likely that a similar reduction would occur for levetiracetam soon after publication of the guideline and that a recommendation without levetiracetam would quickly become inaccurate. They also considered the widespread use of levetiracetam in current clinical practice, based not only on their own experience but also on the feedback of stakeholders during consultation of the guideline. Considering the evidence, the uncertainties and their clinical experience, the GDG therefore determined that levetiracetam should be offered among initial adjunctive therapy options.
Quality of evidence	We extrapolated the evidence from focal seizures for this recommendation. For adults, the majority of the evidence was placebo controlled and there were few head to head comparisons. All of the studies

	were randomised controlled trials, the majority of which were double-blind. Most of the studies gave unclear details of their methods of randomisation, allocation concealment and blinding. The statistically significant results for 50% reduction in seizure frequency were from the placebo-controlled studies. Few of the drugs which were compared to drugswere statistically significant and where this did occur there was uncertainty in the magnitude of clinical effect. The quality overall was generally low or very low. The published economic evidence varied had problems of methodological quality and applicability to the decision-making context of the guideline. Some had out of date costs that could change the study's conclusions or did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.
Other considerations	The drugs recommended above are older and therefore there is long-term experience with them. Eslicarbazepine acetate, lacosamide, pregabalin, and zonisamide showed efficacy but were not included for first-line adjunctive treatment as they are newer drugs and the GDG felt that there needed to be more long-term evidence of their efficacy and cost-effectiveness for adjunctive treatment. There is limited evidence for tiagabine being effective. Gabapentin was included as first-line adjunctive drug option, but based on the clinical experience of the GDG was regarded as less effective than the other AEDs. The GDG considered the addition of oxcarbazepine without trying carbamazepine as unusual but may be considered, as it is less enzyme inducing. The GDG were aware that in clinical practice a second AED is added to the first. They also agreed with published literature which states that if the latter helps the first may be taken away if the patient agrees.[287] GDG discussion centred around some key issues. Namely, care should be taken with clobazam when withdrawing and a slow withdrawal of clobazam over/up to 4-6m in view of the risk of withdrawal seizures. They noted that sodium valproate inhibits the metabolism of lamotrigine and this needs to be taken into consideration when introducing or withdrawing either medication. Clinical experience led the GDG to believe that on withdrawal of sodium valproate, lamotrigine levels may drop and this may be ther reason for breakthrough seizures. They also noted that there should be a concomitant increase in the lamotrigine dose but did not wish to make a specific recommendation. Topiramate may affect phenytoin levels.

Recommendation	**127. If adjunctive treatment (see recommendation 126) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate♣, lacosamide ♣, phenobarbital, phenytoin, pregabalin♣, tiagabine♣, vigabatrin♣ and zonisamide♣. Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields. [new 2012]**
Relative values of different outcomes	In adults and children, achievement of at least a 50% reduction in seizure frequency was an important outcome. These AEDs have evidence of efficacy in some patients, and may benefit patients who have not responded to and /or who have experienced adverse effects with other AEDs.
Trade off between clinical benefits and harms	We extrapolated the results from focal seizures for this recommendation. The balance of benefit and adverse effects needs to be carefully monitored in all patients, and it must be recognised that different individuals may have different responses to various AEDs. From the direct evidence for adults, lacosamide, zonisamide, eslicarbazepine acetate, tiagabine, vigabatrin and pregabalin had more participants with at least 50% reduction in seizure frequency when compared to placebo. Eslicarbazepine acetate, and pregabalin also had more seizure freedom than placebo. Phenobarbital was added by the GDG based on their professional opinion. Tiagabine was found to have no difference when compared to lamotrigine, levetiracetam or phenytoin. In terms of efficacy, there was no significant difference between vigabatrin and gabapentin. Also pregabalin was shown to have a less favourable adverse events profile, causing greater withdrawal due to adverse events than placebo. Eslicarbazepine acetate, lacosamide, vigabatrin, zonisamide and tiagabine had more withdrawal due to adverse events and more adverse events than than placebo arm. There was no difference between phenytoin and tiagabine or lamotrigine and tiagabine for withdrawal due to adverse events. Vigabatrin has a harmful and irreversible side effects profile with retinal toxicity causing visual impairment, according to the GDG expertise and epilepsy literature. These side effects occur over the longer term and would not be observed in any of the short term trials combined in the evidence.

♣ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	A decision model was built to weigh up the clinical benefits of each adjunctive AED, measured by seizure control and seizure reduction, compared to the harms from adverse events as measured by withdrawals from treatment due to adverse events. The drugs recommended for consideration here were effective to varying degress, but the treatment benefits, in terms of QALYs gained, or in some cases lost, did not justified the additional costs over drugs recommended in the previous recommendation (gabapentin, lamotrigine, oxcarbazepine, topiramate).
Economic considerations	We extrapolated the economic considerations from focal seizures for this recommendation. Three economic evaluations were included in the systematic review of published literature (two for adults and one for children), and original economic modelling was undertaken to overcome limitations of and fill in gaps not covered by the published evidence. One published study showed adjunctive zonisamide to be cost-effective compared to adjunctive levetiracetam, but in all other studies and/or in the original modelling work undertaken for the guideline, neither levetiracetam nor zonisamide were shown to be cost-effective compared to alternative AEDs. In the economic analysis undertaken for the guideline, eslicarbazepine acetate, lacosamide, pregabalin, tiagabine and zonisamide were all more costly and less effective than other cost-effective treatment alternatives. Therefore, the GDG felt that they should not be recommended among initial adjunctive therapy options. Rather these drugs should be considered only for cases where previously recommended drugs are contraindicated or have been tried and were either ineffective or not tolerated. Vigabatrin was specifically excluded from various published economic evaluations due to its potential for long term toxicity and adverse effects. It was included in the original economic analysis undertaken for this guideline and was shown to be very effective and cost-effective. However, a very serious limitation of the model was that it did not account for vigabatrin's potential for long term toxicity and development of visual field defects. Vigabatrin's cost-effectiveness in the model was driven by its efficacy and relatively low rates of withdrawal due to adverse events from short term trial data. Had the model accounted for long term, irreversible effects to vision, it is unlikely to have performed quite as well. The GDG recognised its relative effectiveness over other AEDs, and considered the risk of long term visual field defect to outweigh its clinical benefit. The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome.
Quality of evidence	We extrapolated the evidence from focal seizures for this recommendation.

	Overall the quality of evidence was low and most of the studies had unclear or no details of randomisation, allocation concealment or blinding and higher drop-out in the treatment arms. There was no evidence found for phenobarbital but this recommendation is based on GDG expertise. The published economic evidence varied had problems of methodological quality and applicability to the decision-making context of the guideline. Some had out of date costs that could change the study's conclusions or did not include all of the relevant comparators. The original decision models undertaken for the guideline aimed to overcome these limitations, but still had some of their own. Due to this limitation, results concerning vigabatrin's cost-effectiveness were of limited value to GDG decision-making. Limitations of the original analyses, particularly where assumptions had to be made, relate to the lack of data availability on longer term effectiveness and discontinuation, limited health-state utility data and limited to no data to inform estimates of NHS resource use.
Other considerations	The GDG consensus opinion was that management should be discussed with patients or they should be offered referral to, a tertiary epilepsy specialist if adjunctive treatment with AEDs listed in recommendation 127 is ineffective or not tolerated because achieving successful treatment may be complex. They noted that long term experience with some of these drugs (pregabalin, lacosamide, zonisamide and eslicarbazepine acetate) is limited. The GDG discussed the fact that care should be taken when withdrawing phenobarbital and should be slowly withdrawn in view of the risk of withdrawal seizures but did not wish to make a specific recommendation in this area. The group discussed the need for careful evaluation of risk/benefit for each individual to be undertaken for each individual and the final GDG consensus opinion was that vigabatrin should only be prescribed in tertiary epilepsy specialist care.

10.13 Idiopathic Generalised Epilepsy (IGE)

10.13.1 Introduction

The idiopathic generalised epilepsies are a group of epilepsies characterised by typical absences, myoclonic jerks and generalised tonic clonic seizures, alone or in varying combinations in otherwise normal individuals. They probably constitute up to one third of all the epilepsies and are genetically determined. The EEG is characteristic, demonstrating a distinct pattern of generalised polyspike wave discharges and/or generalised spike wave which may be provoked by hyperventilation or sleep deprivation. Some IGEs are associated with photosensitivity.

Depending on the relative prevalence of individual seizure types, the age of onset and frequency of spike wave activity, IGE may be further categorised into individual syndromes. The predominant characteristics of those to be considered in this review are outlined in the table.

This section contains studies that look at idiopathic generalised epilepsies (IGE) (including all) and looking separately on the following subgroups:

- Epilepsy with Tonic-Clonic Seizures only
- Childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes
- Juvenile Myoclonic Epilepsy.

Table 24: Characteristics of the individual syndromes

Epilepsy syndrome	Age of onset	Predominant seizure types/frequency	EEG	Prognosis
Childhood Absence Epilepsy	4-10 years	Absence, many/day GTCS infrequent	3Hz generalised spike and wave	80% remit by adulthood
Juvenile Absence Epilepsy	9-13 years	Absence GTCS in 80% Myoclonic jerks infrequent	3-4Hz generalised spike and wave Photosensitivity 8%	Lifelong; seizure control in 70-80%
Juvenile myoclonic epilepsy	5-16 years	Myoclonic jerks on awakening in all GTCS in most Absence in >30% (may be intial seizure type)	3-6 Hz generalised polyspike and wave Photosensitivity in >30%	Lifelong; seizure control in up to 90% patients
Epilepsy with GTCS only	6-30 years	GTCS 1-2 hours after waking	Generalised polyspike wave in up to 50% patients	Lifelong; seizure control in 90%

10.13.2 Methods of the evidence review of IGE

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with the following syndromes: Absence seizures (childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes), Juvenile Myoclonic Epilepsy and Epilepsy with Tonic-Clonic Seizures only.

10.13.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for IGE. The following interventions were included in our search; clobazam, clonazepam, ethosuximide, lamotrigine, levetiracetam, sodium valproate topiramate and zonisamide. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below are the matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo													
Lamotrigine													
Levetiracetam	1[294]												
Topiramate		1[41]											
Oxcarbazepine													
Phenytoin													
Clobazam													
Clonazepam													
Phenobarbital													
Primidone													
Acetazolamide													
Sodium valproate		2[41],(GlaxoSmithKline unpublished in HTA)[40]		1[41]									
Zonisamide													
Carbamazepine													
	Pla	LTG	LEV	TPM	OXC	PHT	CLB	CZP	PBT	PRM	ACT	VPA	ZN

Matrix of the evidence for IGE

Matrix of the evidence for childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

Placebo									
Lamotrigine	1[319]								
Levetiracetam	1 [320]								
Topiramate									
Ethosuximide		1[321]							
Zonisamide									
Clobazam									
Clonazepam									
Sodium valproate		3[41,321,] (Marson unpub.)		1(Marson unpub.)	4[321,322,323,324]				
	Pla	LTG	LEV	TPM	ETX	ZNS	CLB	CZP	VPA

Matrix of the evidence for Juvenile Myoclonic Epilepsy

Placebo								
Lamotrigine								
Levetiracetam	1[298]							
Topiramate								
Clobazam								
Clonazepam								
Zonisamide								
Sodium valproate		2, [165,](Marson, unpub.)		1[297]; 1(Marson, unpub.)				
	Pla	LTG	LEV	TPM	CLB	CZP	ZNS	VPA

Placebo (Pla) Lamotrigine (LTG) Levetiracetam (LEV) Topiramate (TPM)

Clobazam (CLB) Clonazepam (CZP) Zonisamide (ZNS) Sodium valproate (VPA)

Ethosuximide (ETX) Oxcarbazepine (OXC) Phenytoin (PHT) Phenobarbital (PBT)

Primidone (PRM) Acetazolamide (ACT)

IPD NMA: individual patient data network meta-analyses

10.13.4 Monotherapy for the treatment of IGE in newly diagnosed patients

10.13.4.1 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

Two economic evaluations [161,181] of AEDs, including lamotrigine and sodium valproate, used as monotherapy in the treatment of people with newly diagnosed IGE were identified and included in the economic literature search. The complete results of these studies are presented in section 10.13.6.

Evidence statements

Efficacy – statistically significant results

Sodium valproate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging time to exit/withdrawal (MODERATE QUALITY).

Time to first seizure occurred significantly more rapidly on sodium valproate monotherapy compared to lamotrigine monotherapy. (MODERATE QUALITY)

Time to 12-month remission occurred significantly less rapidly on lamotrigine monotherapy compared to sodium valproate. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the proportion of participants with seizure freedom (VERY LOW QUALITY).

Adverse events - statistically non-significant results

No significant difference between lamotrigine monotherapy versus sodium valproate monotherapy in the proportion of participants withdrawn due to adverse events (VERY LOW QUALITY).

There is no significant difference between lamotrigine monotherapy versus sodium valproate monotherapy in the incidence of:

- tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY).
- other side-effects (please see extraction for full list) (VERY LOW QUALITY).

Quality of Life - statistically significant results

Significantly more participants taking lamotrigine monotherapy compared to sodium valproate monotherapy had higher scores at 2 years on the GQoL questionnaire.

Quality of Life - statistically non-significant results

There is no significant difference between lamotrigine and sodium valproate monotherapy in:

- two year anxiety scores
- two year depression scores
- two year AEP scores
- two year neurotoxicity scale scores
- two year EQ-5D scores

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, lamotrigine monotherapy is more effective than sodium valproate in terms of total QALYs gained and also less costly when using 2010 drug costs. This evidence is directly applicable but has potentially serious limitations.

Evidence from another cost-effectiveness analysis indicates that lamotrigine monotherapy is more costly and less effective than sodium valproate in terms of total QALYs gained. The evidence is directly applicable but as it uses costs from 2001-02, it has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, sodium valproate monotherapy is more costly and more effective at preventing seizures than lamotrigine monotherapy (ICER=£5 per seizure avoided). This evidence is partially applicable and has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- at least a 50% reduction in seizure frequency
- any outcomes relating to cognitive effects.

10.13.4.2 Topiramate versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [161] of AEDs, including topiramate and sodium valproate, used as monotherapy in the treatment of people with newly diagnosed IGE was identified and included in the economic literature search. The complete results of this study are presented in section 10.13.6.

Evidence statements

Efficacy – statistically significant results

Valproate monotherapy is significantly more effective than topiramate monotherapy in prolonging time to exit/withdrawal of allocated treatment (MODERATE QUALITY).

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure (LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to 12-month remission. (VERY LOW QUALITY)

Adverse events-statistically non-significant results

No significant difference between topiramate monotherapy versus sodium valproate monotherapy in the incidence of:

- tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY)
- other side-effects (please see extraction for full list) (VERY LOW QUALITY).

Quality of life -statistically significant results

Significantly more participants taking topiramate monotherapy compared to sodium valproate monotherapy had higher scores at 2 years on the GQoL questionnaire.

Quality of Life – statistically non-significant results

There is no significant difference between sodium valproate monotherapy and topiramate monotherapy in:

- two year anxiety scores
- two year depression scores
- two year AEP scores
- two year neurotoxicity scale scores
- two year EQ-5D scores

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is very likely

to be cost-effective compared with sodium valproate when using 2010 drug costs (ICER=£944 per QALY gained). This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is more costly, but less effective at preventing seizures than sodium valproate monotherapy. This evidence is partially applicable but has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- cognitive outcomes.

10.13.4.3 Lamotrigine versus topiramate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

One economic evaluation [161] of AEDs, including lamotrigine and topiramate, used as monotherapy in the treatment of people with newly diagnosed IGE was identified and included in the economic literature search. The complete results of this study are presented in section 10.13.6.

Evidence statements

Efficacy – statistically significant results

Topiramate monotherapy is significantly more effective than lamotrigine monotherapy in prolonging the time to first seizure, however there is uncertainty over the magnitude of its clinical effect (LOW QUALITY).

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and topiramate monotherapy in the time to exit/withdrawal of allocated treatment (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and topiramate monotherapy in the time to 12-month remission. (VERY LOW QUALITY)

Adverse events– statistically non-significant results

There is no significant difference between lamotrigine monotherapy versus topiramate monotherapy in the incidence of:

- tiredness, drowsiness, fatigue and lethargy (VERY LOW QUALITY).
- other side-effects (please see evidence extraction Appendix L) (VERY LOW QUALITY).

Quality of Life – statistically significant results

Significantly more participants taking lamotrigine monotherapy compared to topiramate monotherapy had higher scores on the GQoL questionnaire.

Quality of Life – statistically non-significant results

There is no significant difference between lamotrigine monotherapy and topiramate monotherapy in:

- two year anxiety scores
- two year depression scores
- two year AEP scores
- two year neurotoxicity scale scores
- two year EQ-5D scores .

Cost-effectiveness

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is very likely to be cost-effective when compared with lamotrigine monotherapy when using 2010 drug costs (ICER=£4,982). This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, topiramate monotherapy is more costly and more effective at preventing seizures than lamotrigine monotherapy (ICER=£11 per seizure avoided). However, sodium valproate monotherapy is most cost-effective in this analysis. This evidence is partially applicable but has potentially serious limitations.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency.
- cognitive outcomes.

10.13.5 Adjunctive therapy in children, young people and adults with IGE

10.13.5.1 Levetiracetam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search, however the NCGC model evaluating adjunctive AEDs in the treatment of adults with refractory generalised tonic-clonic seizures used clinical evidence from this comparison. For results of this analysis, see section 10.5.8.

Evidence statements

Efficacy – statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy were seizure free compared to placebo. (MODERATE QUALITY)

Significantly more participants receiving levetiracetam adjunctive therapy had at least a 50% reduction in seizure frequency compared to placebo. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy versus placebo for the proportion of participants having treatment withdrawn due to adverse events. (VERY LOW QUALITY)

There is no significant difference between levetiracetam adjunctive therapy and placebo for the incidence of:

- nasopharyngitis (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY).

Quality of life – statistically non-significant results

No significant difference between levetiracetam adjunctive therapy and placebo in achieving a greater improvement in the quality of life (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing levetiracetam adjunctive therapy to placebo was identified. However, adjunctive levetiracetam was found to be cost-effective in the treatment of adults with refractory generalized tonic-clonic seizures if adjunctive lamotrigine was not an appropriate clinical option. For details on this evidence, see section 10.5.7.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes.

10.13.6 Health economic evidence for AEDs used as monotherapy in the treatment of patients with newly diagnosed IGE

Two economic evaluations [161,181] assessing the cost-effectiveness of AEDs used as monotherapy in patients with newly diagnosed IGE were identified in the economic literature search and included in the economic evidence review. See appendix M for full study details and assessments of limitations and applicability. These studies were considered sufficient to inform recommendations in this population, therefore no original economic modelling was undertaken.

Economic study characteristics

Table 25: Monotherapy for patients with IGE - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Marson (2007)[161]	Potentially serious limitations (a, b)	Directly applicable (c)	Economic evaluation conducted alongside RCT; comparators included sodium valproate, lamotrigine and topiramate; 2-year time

Study	Limitations	Applicability	Other Comments
			horizon; effect measured as QALYs gained
Marson (2007)[161]	Potentially serious limitations (a, b)	Partially applicable (c, d)	Economic evaluation conducted alongside RCT; comparators included sodium valproate, lamotrigine and topiramate; 2-year time horizon; effect measured as seizures avoided
Hawkins (2005)[181]	Potentially serious limitations (e, f, g)	Partially applicable (h)	Decision analytic model; 15-year time horizon; effectiveness data based on an unpublished study[275]

(a) Sensitivity analysis incomplete in that it only presents comparisons of VPA v LTG and VPA v TPM but fails to present comparison of LTG v TPM.
(b) Unit costs estimates are from 2005.
(c) Study population included patients with IGE (63%) and some patients with an unclassified epilepsy (27%).
(d) Analysis of cost per seizures avoided, not QALYs.
(e) Costs discounted at 3.5% per annum; QALYs discounted 1.5% per annum.
(f) Unit cost estimates are from 2001-2002.
(g) Treatment effects based on results of an unpublished study[275] that was not included in NCGC systematic review.
(h) Did not include all comparators relevant to the guideline review, namely topiramate.

Economic study results

Table 26: Monotherapy for patients with IGE - Economic study characteristics

AED	Total cost (£) per patient	Total effects per patient	ICER	Uncertainty
Cost per QALY analysis		**(QALYs)**	**(£ / QALY)**	
VPA	£1,390	1.648		Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, VPA has a 5% and 37% probability of being cost-effective compared to TPM and LTG respectively. At a willingness to pay threshold of £30,000/QALY, this figure is 97%.
TPM	£1,568	1.809	£1,606	Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, TPM has a 95% probability of being cost-effective compared to VPA. At a willingness to pay threshold of £30,000/QALY, this figure is 97%.
LTG	£1,906 (a)	1.701	Dominated	Bootstrapped estimates indicate that at a willingness to pay threshold of £20,000/QALY, LTG has a 63% probability of being cost-effective compared to VPA. At a willingness to pay threshold of £30,000/QALY, this figure is 68%.
Cost per seizure avoided analysis		**(total seizures)**	**(£/seizure avoided)**	

AED	Total cost (£) per patient	Total effects per patient	ICER	Uncertainty
VPA	£1,136	44.1		Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, VPA has an 84% and 99% probability of being cost-effective compared to TPM and LTG, respectively.
TPM	£1,568	75.1	Dominated	Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, TPM has a 16% probability of being cost-effective compared to VPA.
LTG	£1,761 (a)	120.9	Dominated	Bootstrapped estimates indicate that at a willingness to pay threshold of £1,600/seizure avoided, LTG has a 1% probability of being cost-effective compared to VPA.

(a) Unit costs estimates are from 2005, and since then, unit costs of lamotrigine and topiramate have reduced and may change conclusions of the cost-effectiveness analysis.

As the unit costs of anti-epileptic drugs used in the SANAD trial were from 2005 and the unit costs of lamotrigine and topiramate have changed dramatically since then, it was considered appropriate to update these and perform an incremental analysis based on current AED costs. Current unit costs for lamotrigine, sodium valproate, and topiramate were taken from the BNF 59[325] and a weighted average cost per milligram was calculated based on relative quantities prescribed from the Prescription Cost Analysis 2008[326]. Total drug costs were then combined with the hospitalisation and other costs published in SANAD to calculate a more current average cost per patient. The updated results are presented in table 10.21.

Table 27: Monotherapy for patients with IGE – Results of Marson 2007[161]

AED	Total cost (£) per patient (a)	Total effects per patient	ICER	Uncertainty (b)
Cost per QALY analysis		**(QALYs)**	**(£/QALY)**	
LTG	£1,090	1.701	Dominated	No analysis of uncertainty could be recreated in the update of drug unit costs.
VPA	£1,476	1.648	Dominated	No analysis of uncertainty could be recreated in the update of drug unit costs.
TPM	£1,565	1.809	£4,402	No analysis of uncertainty could be recreated in the update of drug unit costs.
Cost per seizure avoided analysis		**(total seizures)**	**(£/seizure avoided)**	
LTG	£1,090	120.9		No analysis of uncertainty could be recreated in the update of drug unit costs.
VPA	£1,476	44.1	£5	No analysis of uncertainty could be recreated in the update of drug unit costs.
TPM	£1,565	75.1	Dominated	No analysis of uncertainty could be recreated in the update of drug unit costs.

(a) In the published analyses, estimates of total cost were slightly different due to different numbers of patients being included in the cost per QALY and cost per seizure avoided analyses. In this recalculation, they're assumed to have been the same.

(b) Uncertainty is not reflected in these new estimates, as bootstrapped estimates could not be recalculated or cost-effectiveness acceptability curves re-plotted.

(c) Sodium valproate is more costly and more effective in preventing seizures. No explicit willingness to pay per seizure avoided threshold exists to assess the cost-effectiveness of interventions on this measure.

Evidence statements

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, lamotrigine monotherapy is more effective than sodium valproate in terms of total QALYs gained. Using study costs from 2005, lamotrigine is more costly than sodium valproate, but using costs from 2010, lamotrigine is less costly than sodium valproate. This evidence is directly applicable but has potentially serious limitations.

Evidence from one cost-effectiveness analysis conducted alongside a randomised controlled trial shows that in the treatment of idiopathic generalised epilepsy, sodium valproate monotherapy is more effective at preventing seizures than lamotrigine monotherapy. Using study costs from 2005, lamotrigine is more costly than sodium valproate and was thus dominated; using costs from 2010, lamotrigine is less costly than sodium valproate and the ICER for sodium valproate is £5 per seizure avoided. Without an explicit willingness to pay threshold for seizures avoided, the cost-effectiveness of sodium valproate from this analysis is indeterminable. This evidence is partially applicable and has potentially serious limitations.

Table 28: Monotherapy for patients with IGE – Results of Hawkins 2005{Hawkins, 2005 7 /id

AED	Total cost (£) per patient	Total effects (QALYs) per patient	ICER (£/QALY)	Uncertainty
VPA	£4,288	9.814		At a threshold of £30,000 per QALY, VPA has a 95% probability of being optimal.
LTG	£6,675 (a)	9.748	Dominated	At a threshold of £30,000 per QALY, LTG has a 5% probability of being optimal.

(a) The analysis used unit costs from 2001-02. Since then, the cost of LTG has reduced dramatically and may affect conclusions.

Evidence statements

Evidence from a cost-effectiveness analysis indicates that lamotrigine monotherapy is more costly and less effective than sodium valproate in terms of total QALYs gained. The evidence is partially applicable but as it uses costs from 2001-02, it has potentially serious limitations.

10.13.7 Monotherapy for the treatment of childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

10.13.7.1 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in sodium valproate monotherapy were seizure free at one month compared to lamotrigine monotherapy (LOW QUALITY).

Significantly more participants in sodium valproate monotherapy were seizure free at 3-5 month compared to lamotrigine monotherapy (VERY LOW QUALITY).

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for seizure freedom at 12 months (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the proportion of participants who withdrew due to lack of efficacy (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and valproate monotherapy in the time to exit/withdrawal of allocated treatment at 12 months follow-up (VERY LOW QUALITY).

Adverse events – statistically significant results

Significantly more participants in sodium valproate monotherapy had an incidence of sleep problem compared to lamotrigine monotherapy, however there is an uncertainty over the clinical importance of its effect (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of other adverse events (for full list please see evidence extractions Appendix L) at 12 months follow-up (VERY LOW QUALITY).

No significant difference between lamotrigine monotherapy and valproate monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- fatigue (VERY LOW QUALITY)
- hyperactivity (VERY LOW QUALITY)
- hostility (VERY LOW QUALITY)
- personality change (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

Cognitive effect- statistically significant results

Significantly more patients in sodium valproate monotherapy had attentional dysfunction compared to lamotrigine monotherapy at 16-20 weeks follow up (MODERATE QUALITY).

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients and no other economic studies comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with CAE or JAE were identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- outcomes relating to quality of life.

10.13.7.2 Topiramate versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Sodium valproate monotherapy is significantly more effective than topiramate monotherapy in prolonging time to exit/withdrawal of allocated treatment at 12 months follow-up (MODERATE).

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the time to first seizure at 12 months follow-up (VERY LOW QUALITY).

Adverse events – statistically non-significant

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the incidence of tiredness, drowsiness, fatigue and lethargy at 12 months follow-up (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy in the incidence of other adverse events (for full list please see extractions in Appendix L) at 12 months follow-up (VERY LOW QUALITY).

Cost-effectiveness

Evidence of cost-effectiveness could not be extracted from the unpublished data for this subgroup of patients and no other economic studies comparing topiramate monotherapy to sodium valproate monotherapy in a population of patients with CAE or JAE were identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- at least 50% reduction in seizure frequency
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- outcomes relating to quality of life.

10.13.7.3 Sodium valproate versus ethosuximide

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non significant results

No statistically significant difference between ethosuximide monotherapy and sodium valpraote monotherapy on the proportion of seizure free participants (VERY LOW QUALITY).

No statistically significant difference between ethosuximide monotherapy and valproate monotherapy on the proportion of participants achieving at least 50% reduction in seizure frequency (VERY LOW QUALITY).

No statistically significant difference between ethosuximide monotherapy and valproate monotherapy for time to exit/withdrawal of allocated treatment. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more patients on ethosuximide monotherapy had an incidence of nausea, vomiting or both compared to valproic acid monotherapy at 16-20 weeks follow-up (HIGH QUALITY).

Significantly more patients on valproic acid monotherapy had an incidence of hostility compared to ethosuximide monotherapy at 16-20 weeks follow-up; however there is uncertainty over the magnitude of the clinical effect (MODERATE QUALITY).

Significantly more patients on valproic acid monotherapy had an incidence of personality change compared to ethosuximide monotherapy at 16-20 weeks follow-up; however there is uncertainty over the magnitude of the clinical effect (MODERATE QUALITY).

Adverse events – statistically non significant results

No statistically significant difference between ethosuximide monotherapy and valproic acid monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- fatigue (LOW QUALITY)
- headache (LOW QUALITY)
- sleep problem (LOW QUALITY)
- stomach upset (LOW QUALITY)
- hyperactivity (LOW QUALITY)
- vomiting (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)
- initial tiredness (VERY LOW QUALITY)
- decreased number of platelets (without true thrombocytopaenia) (VERY LOW QUALITY)

Cognitive effect- statistically significant results

Significantly more patients on valproic acid monotherapy had attentional dysfunction compared to ethosuximide monotherapy at 16-20 weeks follow up (HIGH QUALITY).

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to ethosuximide monotherapy in a population of patients with CAE or JAE was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- outcomes relating to quality of life.

10.13.7.4 Ethosuximide versus lamotrigine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in ethosuximide monotherapy were seizure free compared to lamotrigine monotherapy (MODERATE QUALITY).

Time to exit/withdrawal of allocated treatment was significantly more rapid in lamotrigine monotherapy compared to ethosuximide monotherapy). (MODERATE QUALITY)

Adverse events – statistically significant results

Significantly more patients in ethosuximide monotherapy had an incidence of nausea, vomiting or both compared to lamotrigine monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (LOW QUALITY).

Significantly more patients in ethosuximide monotherapy had an incidence of stomach upset compared to lamotrigine monotherapy at 16-20 weeks follow-up. However there is uncertainty over the magnitude of the clinical effect (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between ethosuximide monotherapy and lamotrigine monotherapy in the incidence of the following adverse events at 16-20 weeks follow-up:

- fatigue (VERY LOW QUALITY)

- headache (VERY LOW QUALITY).

Cognitive effect- statistically non-significant results

No significant difference between ethosuximide monotherapy and lamotrigine monotherapy in attentional dysfunction at 16-20 weeks follow up (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing ethosuximide monotherapy to lamotrigine monotherapy in a population of patients with CAE or JAE was identified.

Outcomes with no evidence

There were no studies that reported:

- at least 50% reduction in seizure frequency
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to 12-month remission
- outcomes relating to quality of life.

10.13.7.5 Levetiracetam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between levetiracetam and placebo for seizure freedom. (VERY LOW QUALITY)

No significant difference between levetiracetam and placebo for 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between levetiracetam and placebo for withdrawal due to adverse events. (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to 12-month remission

- outcomes relating to adverse events
- outcomes relating to quality of life.

10.13.8 Adjunctive therapy for the treatment of childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

10.13.8.1 Sodium valproate versus ethosuximide

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between valproic acid adjunctive and ethosuximide adjunctive for the proportion of participants with at least 80% reduction in seizure frequency (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing adjunctive valproic acid to adjunctive ethosuximide in a population of patients with CAE or JAE was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure frequency
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events
- outcomes relating to cognitive effects
- outcomes relating to quality of life.

10.13.9 Monotherapy for the treatment of Juvenile Myoclonic Epilepsy (JME)

10.13.9.1 Lamotrigine versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to first seizure was significantly less in children receiving lamotrigine compared to children receiving sodium valproate. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for seizure freedom. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for withdrawal due to lack of efficacy. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for time to exit/withdrawal of allocated treatment. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for withdrawal due to adverse events. (VERY LOW QUALITY)

No significant difference between lamotrigine monotherapy and sodium valproate monotherapy for the incidence of the following adverse events:

- erythematous rash. (VERY LOW QUALITY)
- fatigue. (VERY LOW QUALITY)
- weight increase. (VERY LOW QUALITY)
- tiredness, drowsiness, fatigue or lethargy (VERY LOW QUALITY)
- other adverse events (see evidence extraction Appendix L) (VERY LOW QUALITY)
- outcomes relating to quality of life.

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to sodium valproate monotherapy in a population of patients with JME was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- 50% reduction in seizure frequency
- withdrawal due to lack of efficacy
- cognitive outcomes.

10.13.10 Monotherapy/adjunctive therapy for the treatment of juvenile myoclonic epilepsy (JME)

10.13.10.1 Topiramate versus sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for the proportion of seizure-free participants. (VERY LOW QUALITY).

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy on the proportion of participants experiencing at least a 50% reduction in seizure frequency (50 to <100%) (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy for time to first seizure. (VERY LOW QUALITY).

No significant difference between topiramate monotherapy and sodium valproate monotherapy for time to exit/withdrawal of allocated treatment (VERY LOW QUALITY).

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for withdrawal due to lack of efficacy (VERY LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for withdrawal due to adverse events (VERY LOW QUALITY).

No significant difference between topiramate monotherapy/adjunctive therapy and sodium valproate monotherapy/adjunctive therapy for the incidence of the following adverse events:

- headache (VERY LOW QUALITY)
- concentration/attention difficulty (VERY LOW QUALITY)
- fatigue (VERY LOW QUALITY)
- alopecia (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- paresthesia (VERY LOW QUALITY)
- psychomotor slowing (VERY LOW QUALITY)
- somnolence (VERY LOW QUALITY)
- nausea (VERY LOW QUALITY)

- weight gain (VERY LOW QUALITY)
- appetite increase (VERY LOW QUALITY)
- insomnia (VERY LOW QUALITY)
- abnormal vision (VERY LOW QUALITY)
- rash (VERY LOW QUALITY)
- tiredness, drowsiness, fatigue or lethargy (VERY LOW QUALITY)
- other adverse events (see evidence extraction Appendix L) (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing topiramate monotherapy/adjunctive therapy to sodium valproate monotherapy/adjunctive therapy in a population of patients with JME was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- cognitive outcomes
- outcomes relating to quality of life

10.13.11 Adjunctive treatment for for the treatment of of Juvenile Myoclonic Epilepsy (JME)

10.13.11.1 Levetiracetam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy were myoclonic seizure-free compared to placebo; however, there is uncertainty in the magnitude of the clinical effect (LOW QUALITY).

Significantly more participants receiving levetiracetam adjunctive therapy were seizure free (any seizure subtype); however there is uncertainty in the magnitude of the clinical effect (LOW QUALITY).

Significantly more participants receiving levetiracetam adjunctive therapy achieved 50% or above reduction in myoclonic seizure frequency compared to placebo (MODERATE QUALITY).

Adverse events – statistically non significant results

There is no significant difference between the levetiracetam adjunctive group and the placebo group on the incidence of:

- somnolence (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

Quality of life - statistically significant results

Significantly more participants receiving levetiracetam adjunctive therapy had experienced improvement in health related quality of life compared to placebo (MODERATE QUALITY).

Cost-effectiveness

No economic evidence comparing levetiracetam adjunctive therapy to placebo in a population of patients with JME was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive effects

10.13.12 AEDs for the treatment of epilepsy with generalised tonic clonic seizures only

10.13.13 Introduction

Epilepsy with generalised tonic clonic seizures alone is as described; all individuals have generalised tonic clonic seizures, 17-53% 1-2 hours after awakening. However seizures may also occur during relaxation or leisure, or indeed at other times. It has an age of onset 6-30 years, peak 16-17 years. Interictal EEG shows a normal background with generalised spike wave and multiple spike wave discharges of 2-4 Hz. Seizures may be precipitated by sleep deprivation and excessive alcohol consumption.

10.13.14 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with epilepsy with generalised tonic clonic seizures only.

10.13.15 Matrix of the evidence

Please see section 10.5 in the generalized tonic-clonic seizures evidence review for clinical evidence relating to epilepsy with generalised tonic clonic seizures only.

10.13.16 New recommendations and link to evidence

Idiopathic Generalised Epilepsy (use for unclassified IGE - for specific syndromes see below)

First-Line treatment in children, young people and adults with IGE

Recommendation	**128. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed IGE, particularly if there is a photoparoxysmal response on EEG. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]** **129. Offer lamotrigine[dd] if sodium valproate is unsuitable or not tolerated. Be aware that lamotrigine can exacerbate myoclonic seizures. If JME is suspected see recommendations 134 and 135.[new 2012]**
Relative values of different outcomes	The GDG placed greater importance on efficacy as measured by seizure freedom, withdrawal due to lack of efficacy, time to withdrawal and cost-effectiveness in the trials than the quality of life (measured by EQ5D). EQ5D was undertaken on a small subgroup of individuals and excluded children.
Trade off between clinical benefits and harms	Sodium valproate is the most effective drug for IGE but has disadvantages. The risk of teratogenicity associated with valproate's use is significant, particularly at higher doses, so caution is advised in the use of sodium valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of sodium valproate should be reviewed and options discussed. There was no difference between the proportion of patients achieving seizure freedom or withdrawal due to adverse events. Patients taking topiramate and lamotrigine experienced treatment failure (due to lack of efficacy and adverse events) faster than patients taking sodium valproate. Patients taking sodium valproate had a shorter time to 12 month remission than topiramate or lamotrigine. Sodium valproate was also better at delaying the time to first seizure than lamotrigine. There were no differences between lamotrigine and sodium valproate for incidence of particular adverse events. It is also GDG consensus that lamotrigine is not effective with IGE with photosensitivity. The GDG felt that lamotrigine can be good at treating other IGE seizure types such as GTC seizures but may exacerbate myoclonic seizures. Lamotrigine in high dose (>400mg/day) is associated with increased risk of teratogenicity. Lamotrigine may reduce the concentration of progesterone component of oral contraceptives, so the efficacy of systemic progesterone only methods is reduced. Oestrogens may significantly reduce the concentration of lamotrigine.
Economic considerations	Sodium valproate emerged as the drug most likely to be cost-

[dd] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	effective in the cost per seizure avoided analysis conducted as part of SANAD. Greater weight was given to this analysis as the reduction in seizure frequency is considered to be the most important clinical outcome. The GDG considered the seemingly inconsistent results between the cost per seizure avoided analysis and the cost per QALY gained analysis and concluded that some of the difference may be attributable to the QALY capturing elements of health-related quality of life other than those associated with seizures. Lamotrigine did have a lower rate of withdrawal due to adverse events compared to sodium valproate but this was not statistically significant. Another possible reason for the contradictory result may stem from the fact that QALYs were only measured in adults and total number of seizures was counted for both adults and children. The majority of the patient population in these study arms was under the age of 20, thus the cost per QALY analysis may not be based upon a truly representative sample. Given GDG emphasis on outcomes of effect such as the achievement of seizure freedom/reduction and treatment retention (i.e. avoidance of withdrawal for any reason), sodium valproate is considered to be a drug that produces favourable outcomes to patients and represents good value to the NHS. The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, lamotrigine or topiramate may be cost-effective alternatives. The published economic evidence for the cost effectiveness of lamotrigine and topiramate was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and topiramate has the highest. Patients taking topiramate were reported to enjoy more QALYs and experience fewer seizures than patients taking lamotrigine. Although results would point to topiramate as the most cost-effective drug between the two, other clinical outcomes were also taken into account. In the subgroup of patients with IGE, no statistically significant differences were demonstrated between topiramate and lamotrigine for withdrawal due to adverse events or remission of seizures at 12 months. Although both drugs are likely to be considered cost-effective, the GDG based their recommendation for lamotrigine in preference to topiramate on their clinical experience with the side effect profile of topiramate. If and when topiramate does represent the optimal choice, the clinician and the patient should be aware of topiramate's psychiatric and behavioural side effects.
Quality of evidence	The overall GRADE rating of evidence was moderate or very low quality. The majority of the evidence came from a large, pragmatic, unblinded trial.
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline. Clinicians should consider that VPA may inhibit the hepatic

	metabolism of other drugs and enzyme inducing drugs may enhance the metabolism of VPA.

commendation	***130.*** **Consider topiramate* but be aware that it has a less favourable side-effect profile than sodium valproate and lamotrigine*. [new 2012]**
Relative values of different outcomes	The GDG placed importance on efficacy as measured by time to withdrawal, time to first seizure and time to 12 month remission, adverse events and cost-effectiveness in the trials.
Trade off between clinical benefits and harms	In a comparative trial of sodium valproate verus lamotrigine verus topiramate, sodium valproate was significantly better at prolonging the time to exit compared to topiramate whereas topiramate was significantly better at prolonging time to first seizure than lamotrigine, although there was uncertainty in the magnitude of clinical effect. However topiramate has disadvantages due to drug interactions and its adverse events profile.
Economic considerations	The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, lamotrigine or topiramate may be cost-effective alternatives. The published economic for the cost effectiveness of lamotrigine and topiramate evidence from the SANAD trial was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and topiramate has the highest. Patients taking topiramate were reported to enjoy more QALYs and experience fewer seizures than patients taking lamotrigine. Although results would point to topiramate as the most cost-effective drug between the two, other clinical outcomes were also taken into account. In the subgroup of patients with IGE, no statistically significant differences were demonstrated between topiramate and lamotrigine for withdrawal due to adverse events or remission of seizures at 12 months. Although both drugs are likely to be considered cost-effective, the GDG based their recommendation for lamotrigine in preference to topiramate on their clinical experience with the side effect profile of topiramate. If and when topiramate does represent the optimal choice, the clinician and the patient should be aware of topiramate's psychiatric and behavioural side effects.
Quality of evidence	The overall GRADE rating of evidence was moderate or very low quality. The evidence came from a large, pragmatic, unblended trial.
Other considerations	No other considerations.

Adjunctive treatment in children, young people and adults with IGE

*At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**131. Offer lamotrigine*, levetiracetam*, sodium valproate or topiramate* as adjunctive treatment to children, young people and adults with IGE if first-line treatments (see recommendations 128, 129 and 130) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG based greater importance for this recommendation on seizure freedom and 50% reduction in seizure frequency when levetiracetam used as adjunctive therapy in IGE.
Trade off between clinical benefits and harms	Sodium valproate was shown to be the most effective as monotherapy, but lamotrigine and topiramate were considered reasonable alternatives if sodium valproate was unsuitable. The GDG concluded that given their effectiveness as monotherapy, any of these drugs could be reasonably used in combination with another and should therefore be repeated in the recommendation for adjunctive therapy. Levetiracetam as add on treatment is also an effective adjunctive therapy in IGE and has the advantage of no significant interactions with other medications. There is insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any of these drugs, as adjunctive treatment in patients with IGE. Lamotrigine, sodium valproate and topiramate were all considered cost-effective as monotherapy in the treatment of IGE and this provides some guidance as to their likely cost-effectiveness as adjunctive therapy. The GDG also considered the evidence of cost-effectiveness for lamotrigine, levetiracetam and topiramate as adjunctive treatment for generalised tonic-clonic seizures from the NCGC cost-effectiveness analysis summarised in section 10.5.8 and detailed in appendix S. Many of the studies used in the NCGC economic model included patients with IGE therefore the GDG considered its conclusions applicable to this population as well.
Quality of evidence	Evidence for levetiracetam comes from the data on adjunctive treatment of juvenile myoclonic epilepsy because no adjunctivestudies in IGE were identified and at the time of writing is not currently licensed in monotherapy. The overall GRADE rating of evidence was moderate to very low
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline. Clinicians should be aware that there may be potential problems from withdrawal from these drugs.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**132. If adjunctive treatment (see recommendation 131) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam or zonisamide*. [new 2012]**
Relative values of different outcomes	Reduction in seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	The GDG consensus was that clobazam, clonazepam or zonisamide were possible alternatives in accordance with tertary epilepsy care. The GDG considered it important to mention these drugs as potential options to offer to patients between the time of referral to and consultation with a tertiary specialist. It was thought that these are some of the drugs that a tertiary specialist might use, basing the decision on clinical experience treating patients with refractory generalised seizure types.
Economic considerations	The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome. With regard to the specific drugs listed here, there were no economic evaluations available to inform the GDG on the cost-effectiveness of clobazam, clonazepam or zonisamide.
Quality of evidence	There was no evidence available for IGE for these drugs so this recommendation was based on GDG clinical expertise.
Other considerations	Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Recommendation	**133. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that myoclonic seizures can be aggravated by these medications. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however their

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**133. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
	potential to aggravate IGE makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	There is no evidence of benefit on use of these medications

Juvenile Myoclonic Epilepsy (JME)

First-line treatment in children, young people and adults with JME

Recommendation	**134. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed JME, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG placed most importance on efficacy as measured by seizure freedom, time to first seizure, time to withdrawal and adverse events in JME.
Trade off between clinical benefits and harms	The evidence for monotherapy treatment of juvenile myoclonic epilepsy is very limited, predominantly based on a single unpublished subgroup analysis. Results indicate that sodium valproate was more effective than lamotrigine although there was no significant difference observed in terms of treatment failure. No difference was observed between topiramate and sodium valproate, although results for all outcomes trended towards sodium valproate being more effective. Although sodium valproate is more effective than lamotrigine and may be more effective than topiramate in the treatment of JME, it has certain disadvantages. The risk of teratogenicity associated with the use of valproate is significant, particularly at higher doses, so caution is advised in the use of sodium valproate in women of childbearing potential. In girls whose seizures continue and who are approaching child bearing potential, the continued use of sodium valproate should be reviewed and options discussed.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat patients with JME. However, the GDG drew from the cost-effectiveness evidence for sodium valproate in idiopathic generalised epilepsy as a whole. On this basis, they put greater emphasis on the cost per seizure avoided analysis from SANAD because reduction of seizure frequency is considered to be the most important clinical outcome.
Quality of evidence	There was limited evidence for JME monotherapy. Only three unblinded studies were found with overall GRADE rating of evidence moderate to very low quality. Two of these studies had very small samples (one was a pilot study whereas the other was a

Recommendation	**134. Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed JME, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
	subgroup which the authors did not analyse statistically due to the small number and imbalance of distribution. The other larger unblinded study (SANAD) found only sodium valproate to have longer time to first seizure than lamotrigine.
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline. Clinicians should consider that VPA may inhibit the hepatic metabolism of other drugs and enzyme inducing drugs may enhance the metabolism of VPA.

Recommendation	**135. Consider lamotrigine*, levetiracetam*, or topiramate* if sodium valproate is unsuitable or not tolerated. Be aware that topiramate has a less favourable side-effect profile than lamotrigine, levetiracetam and sodium valproate, and that lamotrigine may exacerbate myoclonic seizures. [new 2012]**
Relative values of different outcomes	The GDG placed greatest importance on efficacy as measured by seizure freedom, time to first seizure and time to withdrawal in JME.
Trade off between clinical benefits and harms	The GDG felt that lamotrigine may be good at treating other JME seizure types such as GTC seizures but may exacerbate myoclonic seizures. Lamotrigine in high dose (>400mg/day) is associated with increased risk of teratogenicity. Lamotrigine may reduce the concentration of progesterone component of oral contraceptives, so the efficacy of systemic progesterone only methods is reduced. Oestrogens may significantly reduce the concentration of lamotrigine. It is the GDG consensus that topiramate has not been shown to be effective in IGE with photosensitivity. There are limited data on the safety of topiramate in pregnancy and at present the risk appears overall similar to lamotrigine. Topiramate particularly at higher doses may reduce the efficacy of the combined oral contraceptive. Due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, the GDG felt it is not a drug of first choice where other drugs are suitable. At the time of writing this guideline, levetiracetam is not licensed for monotherapy in the UK. It has been shown to be effective as adjunctive therapy in juvenile myoclonic epilepsy and has the advantage of having no significant reported interactions with other medications. Further, the GDG experience is that it has a very favourable side effect profile. It has been demonstrated to be effective for photosensitivity (in a phase II trial of 12 photosensitive patients by Kasteleijn-Nolst in 1996). The GDG decided to recommend off-label use of levetiracetam for juvenile myolonic epilepsy as the evidence for efficacy and tolerability in adjunctive therapy concurred with their clinical experience of its use in monotherapy. Additionally, given the particular adverse events associated with alternative first line drugs for juvenile myoclonic epilepsy, the GDG felt there to be a need for more options. At the time of writing the guideline, there is insufficient data to judge the safety of levetiracetam in

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

	pregnancy.
Economic considerations	The GDG considered that there are patients for whom sodium valproate is contraindicated or not tolerated and for these patients, lamotrigine or topiramate may be cost-effective alternatives. The published economic evidence for the cost effectiveness of lamotrigine and topiramate in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and topiramate has the highest, with both likely to be considered cost effective. GDG experience was that lamotrigine's potential to exacerbate myoclonic seizures in some patients may make it less or not cost-effective as aggravation of seizures is likely to negatively impact health-related quality of life and increase use of NHS resources. However, lamotrigine should not be ignored as a possible treatment option as it can be helpful in controlling other seizure types commonly experienced by patients with JME. There is currently no evidence on which to assess the cost-effectiveness of levetiracetam as a monotherapy in patients with JME. In the absence of any applicable economic evidence, the GDG considered the cost-effectiveness results of levetiracetam as a monotherapy in a population with focal epilepsy where it was more effective than topiramate and also had a slightly lower total cost over the entire 15-year time horizon. In addition, the GDG looked to the results of the decision model undertaken to evaluate adjunctive therapies in a population with refractory generalised tonic-clonic seizures, where levetiracetam was also less costly and more effective than topiramate. However, in both of these models, lamotrigine is more cost-effective than levetiracetam and topiramate. But given the potential problems of lamotrigine in patients with JME, the GDG considered it less likely to be as cost-effective here. On the assumption that levetiracetam is at least as effective as topiramate in the treatment of JME, the GDG concluded that, as observed in other populations, it was likely to represent reasonable value to the NHS when sodium valproate and lamotrigine are unsuitable treatment options. Research into both the effectiveness and cost-effectiveness of levetiracetam as a monotherapy in this population is essential to reduce the substantial uncertainty in this decision.
Quality of evidence	There was limited evidence for JME monotherapy. Only three unblinded studies were found with overall GRADE rating of evidence moderate to very low quality. Two of these studies had very small samples (one was a pilot study whereas the other was a subgroup which the authors did not analyse statistically due to the

	small number and imbalance of distribution. The other larger unblinded study (SANAD) found only sodium valproate to have longer time to first seizure than lamotrigine. Data for levetiracetam as adjunctive therapy came from a study where all participants had myoclonic seizures and a high percentage had juvenile myoclonic seizures. GDG opinion was also used to inform recommendations.
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Adjunctive treatment in children, young people and adults with JME

Recommendation	**136. Offer lamotrigine*, levetiracetam, sodium valproate or topiramate* as adjunctive treatment to children, young people and adults with JME if first-line treatments (see recommendations 134 and 135) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	50% seizure reduction and adverse effects were considered the most important outcomes.
Trade off between clinical benefits and harms	Levetiracetam is effective as adjunctive therapy in myoclonic seizures and has the advantage of no significant interactions with other medications. There are insufficient data to judge the safety of levetiracetam in pregnancy at the time of writing the guideline. Lamotrigine, sodium valproate and topiramate are effective for JME monotherapy and the GDG consensus was that they were appropriate for use as adjunctive therapy.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of levetiracetam or topiramate as a treatment specifically in patients with JME. The clinical evidence for adjunctive levetiracetam in a population with JME shows it to be even more effective compared to placebo than in a population with primary generalised tonic-clonic seizures. On that basis, the GDG felt that the cost-effectiveness of adjunctive levetiracetam was likely to be the same or better than in the analysis conducted for patients with generalised tonic-clonic seizures, summarised in section 10.5.8 and detailed in appendix S. In the same analysis, topiramate was not shown to be cost-effective, but in the event that adjunctive levetiracetam fails to produce the desired reduction in seizure frequency, the GDG felt that it could be considered.
Quality of evidence	The overall GRADE quality rating for the evidence of levetiracetam as adjunctive therapy was was moderate to very low quality.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**136. Offer lamotrigine*, levetiracetam, sodium valproate or topiramate* as adjunctive treatment to children, young people and adults with JME if first-line treatments (see recommendations 134 and 135) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
	However there was only one double-blind study of IGE with myoclonic seizures where 93.4% had juvenile myoclonic epilepsy and 6.6% had juvenile absence epilepsy.
Other considerations	For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

Recommendation	**137. If adjunctive treatment (see recommendation 136) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam or zonisamide*. [new 2012]**
Relative values of different outcomes	Reduction in seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	The GDG consensus was that clobazam, clonazepam or zonisamide were possible alternatives in accordance with tertary epilepsy care. The GDG considered it important to mention these drugs as potential options to offer to patients between the time of referral to and consultation with a tertiary specialist. It was thought that these are some of the drugs that a tertiary specialist might use, basing the decision on clinical experience treating patients with refractory generalised seizure types.
Economic considerations	The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome. With regard to the specific drugs listed here, there were no economic evaluations available to inform the GDG on the cost-effectiveness of clobazam, clonazepam or zonisamide.
Quality of evidence	There was no evidence available for JME for these drugs so this recommendation was based on GDG clinical expertise.
Other considerations	Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6 months in view of the risk of withdrawal seizures. For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**137. If adjunctive treatment (see recommendation 136) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam or zonisamide*. [new 2012]**

Recommendation	**138. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that JME can be aggravated by these medications. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population, however their potential to aggravate JME makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	There is no evidence of benefit on use of these medications

Epilepsy with generalised tonic clonic (GTC) seizures only
First-line treatment in children, young people and adults with newly diagnosed epilepsy with GTC seizures only

Recommendation	**139. Offer lamotrigine or sodium valproate as first-line treatment to children, young people and adults with epilepsy with GTC seizures only. If they have suspected myoclonic seizures, or are suspected of having JME, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	In the evidence for epilepsy with generalised tonic clonic seizures only there was no significant difference between lamotrigine, sodium valproate and topiramate in terms of time to treatment failure or time to first seizure. In extrapolated evidence from generalised tonic-clonic seizures there was no significant difference in the proportion of participants achieving seizure freedom between sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. There were few significant differences in the direct evidence for efficacy and for most comparisons in the IPD analyses. However sodium valproate was significantly better than Phenobarbital, topiramate and carbamazepine for time to withdrawal. Phenytoin and sodium valproate were significantly better than lamotrigine for time to first seizure. Phenytoin, carbamazepine, sodium valproate and topiramate were significantly better than lamotrigine for time to 12 month remission. The GDG consensus opinion was that there is a tendency for drugs such as carbamazepine and oxcarbazepine to exacerbate certain seizures types such as myoclonic and absence seizures. Therefore, they concluded that although there is evidence to support the role of carbamazepine and oxcarbazepine in the treatment of generalised tonic-clonic seizures, they should only be considered once other seizure types have had time to present following initiation of first-line drugs. The GDG considered that due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, it is not a drug of first choice where other drugs are as effective. Sodium valproate and high dose lamotrigine are associated with an increased risk of neural tube and other defects and so the women of child-bearing age should be informed of such risks. The GDG considered that the benefits of reduction of seizures outweighed the adverse effects.
Economic considerations	No economic evidence was identified in the literature and no economic evaluation was undertaken to inform the cost-effectiveness of first line AEDs used to treat newly diagnosed patients experiencing generalised tonic-clonic seizures. The GDG

	felt that an extrapolation from the SANAD study population with generalised epilepsies to a population with generalised tonic-clonic seizures was appropriate and that the relative cost-effectiveness of sodium valproate was unlikely to be different between these groups. Sodium valproate emerged as the drug most likely to be cost-effective in the cost per seizure avoided analysis conducted as part of the SANAD trial[161]. Greater weight was given to this analysis as the reduction in seizure frequency, particularly of generalised tonic-clonic seizures, is considered to be the most important clinical outcome. The published economic evidence for the cost effectiveness of lamotrigine in patients with IGE was out of date and a rough re-estimation based on current costs was undertaken. The new results indicate that lamotrigine has the lowest total cost and is also likely to be considered cost-effective.
Quality of evidence	The evidence for epilepsy with generalised tonic clonic seizures only had an overall GRADE quality rating of low to very low. The evidence came from a large, pragmatic, unblinded trial and no significant differences were found. Further evidence was extrapolated from the GTC seizures data. There was a lack of power of studies particularly with regard to adverse events. The overall quality of evidence was very low with poor reporting of randomisation methods, allocation concealment and many studies were unblinded. There was a high drop-out rate in the majority of studies. Time to event data was available from a network meta-analysis of individual patient data.
Other considerations	Diagnostic, demographic and dosing considerations must be taken into consideration. Phenytoin was shown to have efficacy but the GDG considered it to have a very high adverse events profile. Sodium valproate inhibits the metabolism of lamotrigine and this must to be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in the lamotrigine dose. The GDG is aware that levetiracetam is widely used in current practice as a first-line monotherapy in the treatment of newly diagnosed generalised tonic-clonic seizures, particularly when sodium valproate is unsuitable. There was much debate as to whether levetiracetam should be recommended alongside or in preference to lamotrigine, especially considering lamotrigine's potential to exacerbate myoclonic seizures that may or may not have previously presented. However, the GDG's final decision not to recommend levetiracetam as first line monotherapy in this group of patients is in accordance with NICE methodology which states that 'use for an indication for which the product does not have a marketing authorization may be recommended if there is clear evidence to support this.' Levetiracetam is not currently licensed as monotherapy in the treatment of generalised epilepsies and no randomised controlled trial evidence was identified to demonstrate its effectiveness compared to alternative drugs.

	Furthermore, in the absence of such evidence it is impossible to measure levetiracetam's relative cost-effectiveness compared to other demonstrably cost-effective AEDs used to treat tonic-clonic seizures. Consequently, levetiracetam is recommended as adjunctive therapy, where evidence is available to demonstrate its clinical and cost-effectiveness. The GDG considered it important to direct users of the guideline to the recommendations for the treatment of myoclonic seizures and juvenile myoclonic epilepsy where other drugs, including topiramate and levetiracetam, may be considered if sodium valproate or lamotrigine are unsuitable.

Recommendation	**140. Consider carbamazepine and oxcarbazepine* but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]**
Relative values of different outcomes	In children, young people and adults, seizure-freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	There was limited evidence available for first-line treatment of newly diagnosed epilepsy with GTC seizures only so the evidence was extrapolated from the GTC seizures review. In adults, there was no significant difference in seizure freedom between sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. In children there was no difference between sodium valproate and carbamazepine. The GDG consensus opinion reflects widespread clinical experience that drugs such as carbamazepine and oxcarbazepine may exacerbate certain seizures types, and specifically myoclonic and absence seizures. Therefore, they concluded that although there is evidence to support the role of carbamazepine and oxcarbazepine in the treatment of generalised tonic-clonic seizures, they should only be considered once other seizure types have had time to present following initiation of first-line drugs. Carbamazepine and oxcarbazepine are associated with an increased risk of congenital defects and so the women of child-bearing age should be informed of such risks.
Economic considerations	No economic evidence for carbamazepine or oxcarbazepine in a population with epilepsy with generalised tonic clonic seizures only or generalised epilepsy was available. The GDG considered their relative cost-effectiveness compared to sodium valproate and lamotrigine in populations with focal epilepsy and concluded that it might be broadly similar. However, the GDG considered that carbamazepine and oxcarbazepine may aggravate other seizure types, thus negatively impacting patient quality of life and potentially increasing NHS resource use. On this basis, they felt it would be a more efficient use of NHS resources to consider these

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**140. Consider carbamazepine and oxcarbazepine* but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]**
	AEDs only after lamotrigine or sodium valproate have been tried and other seizure types have had time to present.
Quality of evidence	Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power of studies particularly with regard to adverse events. The overall quality of evidence was very low with poor reporting of randomisation methods, allocation concealment and many studies were unblinded. There was a high drop-out rate in the majority of studies.
Other considerations	No other considerations.

Adjunctive treatment in children, young people and adults with newly diagnosed epilepsy with generalised tonic clonic (GTC) seizures only

Recommendation	**141. Offer clobazam*, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with epilepsy with GTC seizures only, if first-line treatments (see recommendation 139 and 140) are ineffective or not tolerated. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The most important outcomes were adverse effects and 50% reduction in seizure frequency.
Trade off between clinical benefits and harms	There was no evidence available for adjunctive treatment of newly diagnosed epilepsy with generalised tonic clonic seizures only so the evidence was extrapolated from the GTC seizures review. Lamotrigine, levetiracetam and topiramate as adjunctive therapies all significantly reduced seizure frequency by at least 50% when compared to placebo. There was significantly more seizure freedom with clobazam and levetiracetam compared to placebo but lamotrigine and topiramate showed no difference compared to placebo. There was no significant difference for any adverse event, withdrawal due to adverse events or lack of efficacy for lamotrigine, levetiracetam and topiramate adjunctive therapies when compared to placebo.
Economic considerations	The GDG considered the evidence from the economic evaluation undertaken for the guideline in which lamotrigine emerged as a very cost-effective adjunctive therapy in patients experiencing refractory generalised tonic-clonic seizures. If lamotrigine had been tried previously, levetiracetam was also likely to be a cost-effective adjunctive AED. Topiramate was not shown to be cost-effective, but in the event that other alternatives fail to produce

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	the desired reduction in seizure frequency, the GDG felt that it should be considered. Clobazam was not evaluated as part of the cost-effectiveness analysis because the clinical studies did not report all outcomes necessary for inclusion. However, the GDG considered that its effectiveness compared to placebo and its small unit cost is likely to make it cost-effective.
Quality of evidence	Diagnostic, demographic and dosing considerations must be taken into consideration. There was a lack of power in the studies particularly with regard to side-effects. The overall quality of evidence was low: some had no details of randomisation or allocation concealment, high drop-out rate or a very small sample size.
Other considerations	There is a pharmacodynamic interaction between levetiracetam and carbamazepine and between lamotrigine and carbamazepine so side effects may be enhanced. Sodium valproate inhibits the metabolism of lamotrigine and this must be taken into consideration when introducing or withdrawing either medication. On withdrawal of sodium valproate, lamotrigine levels may drop and this may be the reason for breakthrough seizures. There should be a concomitant increase in lamotrigine dose. Care should be taken when withdrawing clobazam with a slow withdrawal up to 4-6m in view of the risk of withdrawal seizures. Topiramate may affect phenytoin levels.

Childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

First-line treatment in children, young people and adults with childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

Recommendation	***142.*** **Offer ethosuximide or sodium valproate as first-line treatment to children, young people and adults with absence syndromes. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable. Be aware of teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that the different side effect profiles of sodium valproate and ethosuximide could not determine which one of these drugs be used first, although there may be individual factors that may determine the choice of one drug over the other. Significantly more patients on sodium valproate showed difficulties in attention. Caution should be used with sodium valproate in girls of child bearing potential.
Economic considerations	No economic evaluations were available to inform the GDG on the

	cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. At the time the GDG considered the evidence, there were significant cost differences between ethosuximide capsules (£0.68 per 250 mg) and ethosuximide syrup (£0.108 to £0.165 per 250 mg). According to the Prescription Cost Analysis of 2008, 99.7% of ethosuximide prescriptions were for syrup. When ethosuximide syrup is prescribed, the daily unit costs of ethosuximide and sodium valproate are very comparable. On this basis the GDG considered that clinical judgement and patient choice should guide the decision for which of the likely cost-effective drugs to offer.
Quality of evidence	The evidence base for this recommendation was retrieved from a double blinded study of a very good quality, a double-blinded of unclear/low quality and from two unblinded studies. A blinded study was found for juvenile absence epilepsy for levetiracetam versus placebo which found no significant differences, however this study lasted 14 days.
Other considerations	The GDG considered that the data available for childhood absence epilepsy can be extrapolated to those individuals with juvenile absence epilepsy, and also to those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.

Recommendation	***143.*** **Offer lamotrigine* if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that the side effect profile of lamotrigine was more favourable, but its efficacy was less favourable, when compared with ethosuximide and sodium valproate.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used to treat CAE, JAE or generalised absence seizures. The GDG considered that at recommended daily doses lamotrigine, sodium valproate and ethosuximide syrup have broadly similar unit costs, but that lamotrigine was less effective than sodium valproate and ethosuximide in this population. But if sodium valproate and/or ethosuximide do not produce the clinical benefit desired, the GDG felt that lamotrigine was a potentially cost-effective alternative.
Quality of evidence	The evidence base was retrieved from a double blinded study of very good quality and from two unblinded studies.
Other considerations	The GDG considered that the data available for CAE can be extrapolated to those individuals with JAE, and those who have generalised absence seizures but who do not meet the criteria for childhood absence epilepsy or juvenile absence epilepsy.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Adjunctive treatment in children, young people and adults with childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes

Recommendation	***144.*** **If two first-line AEDs (see recommendations 142 and 143) are ineffective in children, young people and adults with absence epilepsy syndromes, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine[*] or sodium valproate. Be aware of the teratogenic risks of sodium valproate (see recommendation 83). [new 2012]**
Relative values of different outcomes	The GDG considered seizure freedom, reduction in seizure frequency and adverse events to be the most important outcomes for this recommendation.
Trade off between clinical benefits and harms	The GDG considered that if at least two of the first line AEDs have failed to produce the desired effect (seizure freedom), then it is appropriate to try a well tolerated combination of two of them. Although there is no evidence in this population specifically, GDG experience is that any of the three can be safely combined and given their effectiveness as individual drugs, the expectation is that they are effective in combination. Caution should be used with sodium valproate in girls of child bearing potential.
Economic considerations	No economic evaluations were available to inform the GDG on the cost-effectiveness of any AEDs used as monotherapy or adjunctive therapy to treat CAE, JAE or generalised absence seizures. There was no evidence to suggest that any specific combination of ethosuximide, lamotrigine and sodium valproate is better than another. Any combination is expected to be broadly similar in terms of cost as well. Therefore, the GDG considered that clinical judgement and patient choice should guide the decision for which of the likely cost-effective AED combinations to offer.
Quality of evidence	The evidence base for this recommendation was extrapolated from the evidence for each of these drugs as monotherapy in newly diagnosed absence seizures and was supported by GDG consensus.

[*] At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**145. If adjunctive treatment (see recommendation 144) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam*, clonazepam, levetiracetam*, topiramate* or zonisamide*. [new 2012]**
Relative values of different outcomes	Reduction in seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	The GDG consensus was that clobazam, clonazepam, topiramate or zonisamide were possible alternatives in accordance with tertiary epilepsy care. The GDG considered it important to mention these drugs as potential options to offer to patients between the time of referral to and consultation with a tertiary specialist. It was thought that these are some of the drugs that a tertiary specialist might use, basing the decision on clinical experience treating patients with childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes. There was no difference found for topiramate and sodium valproate for time to first seizure from sodium valproate but topiramate had a shorter time to withdrawal. Due to the seriousness of side effects reported for topiramate such as psychiatric and behavioural changes reported in the SANAD trial, the GDG felt it is not a drug of first choice where other drugs are suitable.
Economic considerations	The GDG recommended that these patients should be discussed with or referred to a tertiary epilepsy specialist. Whilst this may be more costly, the GDG considered that this was worthwhile as these patients may require more complex care in order to achieve a successful outcome. With regard to the specific drugs listed here, there were no economic evaluations available to inform the GDG on the cost-effectiveness of clobazam, clonazepam, topiramate or zonisamide.
Quality of evidence	There was no evidence available for childhood absence epilepsy, juvenile absence epilepsy and other absence epilepsy syndromes for clobazam, clonazepam and zonisamide so these drugs were added to this recommendation based on GDG clinical expertise. There was limited evidence available for topiramate from a large unblinded pragmatic trial.
Other considerations	Care should be taken with clobazam and clonazepam due to a slow withdrawal up to 4-6m in view of the risk of withdrawal seizures. For further guidance on medication adherence to refer to the NICE Medicines Adherence guideline.

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**146. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effects were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Clinical practice suggests that absence seizures can be aggravated by these medications, and can compromise cognition with risk of nonconvulsive status epilepticus. The GDG felt that use of these medications would lead to no clinical benefit and could cause harm.
Economic considerations	No economic evidence was available to inform the cost-effectiveness of these AEDs in this population; however their potential to aggravate absence seizures makes them very unlikely to be cost-effective. Aggravation of seizures is likely to negatively impact health-related quality of life and increase NHS resource use.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	There is no evidence of benefit on use of these medications

10.14 Other epilepsy syndromes

10.14.1 Introduction

There remain further epilepsy syndromes with recognizable characteristic electroclinical features in which natural history and prognosis are known. Many of these syndromes are rare and evidence base with regard to their management lacking. In view of this, in many individuals management may be continued under tertiary paediatric neurology care.

Clinical evidence

No evidence was retrieved for other epilepsy syndromes.

Health Economic Evidence

No studies were identified in the economic literature search.

10.14.2 New recommendations and link to evidence

Recommendation	**147. Refer to a tertiary paediatric epilepsy specialist all children and young people with continuous spike and wave during slow sleep, Landau–Kleffner syndrome or myoclonic-astatic epilepsy. [new 2012]**
Relative values of different outcomes	Many children with these syndromes are very unlikely to achieve seizure freedom. The children usually have additional learning disabilities. Optimal seizure control without unacceptable side effects was therefore the most important outcome for this recommendation.
Trade off between clinical benefits and harms	No RCT studies were found and therefore this recommendation is based on the consensus opinion of the GDG. These syndromes, if untreated, can lead to significant cognitive impairment and reduced educational potential, with a high risk of co-morbidities. The GDG felt that it was important that these children be referred to a tertiary epilepsy specialist to manage their care.
Economic considerations	No economic evidence was available to inform recommendations in groups with CSWS, LKS or MAE.
Quality of evidence	No RCT data was available for any of these syndromes. This recommendation is based on GDG consensus opinion.
Other considerations	None.

10.14.3 New research recommendations (for full list see section 2.11)

10.14.3.1 Epilepsy Syndromes

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

Why this is important

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

The research should include:

- multicentre randomised controlled comparative trials with centralised national data collection
- the ketogenic diet as one of the randomised treatments
- primary outcome of seizure freedom
- secondary outcomes, including seizure reduction, quality of life and cognitive outcome
- an attempt to obtain data on pharmaco-resistance
- the possibility of including all children with specific epilepsy syndromes for consideration in the trial.

10.15 Prolonged seizures and convulsive status epilepticus

10.15.1 Introduction

Generalised seizures (TC, tonic, clonic)

In the past, status epilepticus (SE) was defined as a seizure lasting longer than 30 minutes or two or more seizures within 30 minutes without a return to the baseline level of consciousness between seizures. More recently, the definition evolved to be a seizure longer than 5 minutes or two or more seizures without a return of consciousness between seizures [327]. Serial seizures are defined as 3 or more tonic clonic seizures in an hour.

SE can be divided into a number of subtypes, either by seizure type or by response to treatment. Clinical SE can be either focal or generalised, and each of these types can be divided by duration:

- early SE (5-30 minutes)
- established SE (>30 minutes)
- refractory SE (seizures persist despite treatment with adequate doses of two or three initial anticonvulsant medications) [327].

The BNF states that: immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of high flow oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine should be considered if alcohol abuse is suspected; pyridoxine should be given if the status epilepticus is caused by pyridoxine deficiency.

Convulsive SE should be treated urgently with intravenous lorazepam, repeated once after 10 minutes if seizures recur. Intravenous diazepam is effective but it is associated with a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Intravenous clonazepam can also be used as an alternative.

Where facilities for resuscitation are not immediately available, diazepam can be administered rectally or **midazolam** can be given into the buccal cavity.

It is important that if seizures recur or fail to respond within 30 minutes, phenytoin sodium, fosphenytoin, or phenobarbital sodium should be used. If these measures fail to control seizure within 60 minutes, anaesthesia with thiopental, midazolam , or in adults, a non-barbiturate anaesthetic such as propofol [unlicensed indication], should be instituted with full intensive care support.

Phenytoin sodium may be given by slow intravenous injection, with ECG monitoring, followed by the maintenance dosage. Intramuscular use of phenytoin is not recommended (absorption is slow and erratic).

In theory, fosphenytoin, a pro-drug of phenytoin, when given intravenously causes fewer injection-site reactions than phenytoin. Intravenous administration requires ECG monitoring. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin should be expressed in terms of phenytoin sodium.

Paraldehyde still has a limited place. It remains a valuable anticonvulsant but in limited situations as it may prove effective when other anticonvulsants have failed to terminate the seizure. Given rectally it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

10.15.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included people with prolonged seizures and convulsive status epilepticus.

10.15.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacological interventions for people with prolonged seizures and convulsive status epilepticus. The following interventions were included in our search; lorazepam, diazepam, midazolam, clonazepam, paraldehyde, phenytoin, fosphenytoin, phenobarbital, propofol, thiopental, isoflurane, sodium valproate, levetiracetam, phentobarbital and lidocaine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified separately for adults and children. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Matrix of the evidence for the treatment of convulsive status epilepticus in adults (community)

Placebo	
Intravenous lorazepam	1[328]

Intravenous diazepam	1[328]			
Rectal/Intravenous diazepam		1[328]		
	Pla	R IV LZP	IV DZP	R IV DZP

Matrix of the evidence for the treatment of convulsive status epilepticus in children (community)

Placebo			
Buccal/intranasal midazolam			
Rectal/Intravenous diazepam		4[329-331, 332]	
	Pla	B/IN MDM	Rectal/IV diazepam

Matrix of the evidence for the treatment of acute repetitive seizures (children and adults)

Placebo		
Diazepam gel	2*[333,334]	
	Pla	Diazepam gel

Matrix of the evidence for the treatment of convulsive status epilepticus in adults (initial treatment in Accident and Emergency (A+ E))

Placebo					
Intravenous lorazepam					
Intravenous diazepam		1[335]			
Intravenous diazepam and phenytoin		1[336]			
Intravenous phenytoin		1[336]		1[336]	

Intravenous phenobarbital		1[336]		1[336]	1[336]			
Intravenous phenobarbital and phenytoin				1[337]				
Intravenous sodium valproate					2*[338, 339]			
	Pla	IV LZP	IV DZP	IV DZP, PHT	IV PHT	IV PBT	IV PBT, PHT	IV VPA

Matrix of the evidence for the treatment of convulsive status epilepticus in children (initial treatment in ER)

Placebo							
Buccal/intranasal midazolam							
Rectal/Intravenous diazepam		3[329-331]					
Intramuscular midazolam							
Intravenous diazepam				1[340]			
Intranasal lorazepam							
Intramuscular paraldehyde						1[341]	
	Pla	B IN MDM	R IV DZP	IM MDM	IV DZP	IN LZP	IM PLH

Matrix of the evidence for the treatment of refractory status epilepticus in children

Placebo						
Intravenous diazepam						
Intranasal lorazepam						
Sodium valproate infusion		1[342]				

Midazolam infusion										
Diazepam infusion					1[343]					
Rectal sodium evaporate					1[344]					
Intravenous Midazolam										
Intravenous lidocaine					1[345]					
Intravenous propofol					1[346]					
	Pla	IV DZP	IN LZP	VPA IF	MDM IF	DZP IF	R VPA	IV MDM	IV LID	IV PRF

Placebo (Pla) Diazepam gel (DZP gel) Intravenous lorazepam (IV LZP) Rectal/Intravenous lorazepam (IV LZP)
Intravenous diazepam (IV DZP) Rectal/Intravenous diazepam (R IV DZP) Intravenous phenytoin (IV PHT)
Intravenous diazepam and phenytoin (IV DZP, PHT) Intravenous phenobarbital (IV PBT)
Intravenous phenobarbital and phenytoin (IV PBT, PHT) Intravenous sodium valproate (IV VPA)
Buccal/Intranasal midazolam (B IN MDM) Rectal/Intravenous diazepam (R IV DZP) Intramuscular midazolam (IM MDM)
Intranasal lorazepam (IN LZP) Rectal sodium valproate (R VPA) Intramuscular paraldehyde (IM PLH) Intravenous diazepam (IV DZP)
Intravenous propofol (IV PRF) Intravenous midazolam (IV MDM) Sodium valproate infusion (VPA IF) Diazepam infusion (DZP IF)
Midazolam infusion (MDM IF)

10.15.4 AEDs for the treatment of prolonged seizures and convulsive status epilepticus in the community

148. Care must be taken to secure the child, young person or adult's airway and assess his or her respiratory and cardiac function. [2004]

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

10.15.4.1 Intravenous diazepam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more patients receiving intravenous diazepam were seizure free compared to placebo. (HIGH QUALITY)

Adverse events – statistically significant results

Intravenous diazepam was associated with a significantly lower incidence of death than placebo, however there is uncertainty of the magnitude of the effect. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between intravenous diazepam and placebo for the incidence of:

- hypotension, cardiac dysrhythmia or respiratory intervention (MODERATE QUALITY)
- the proportion of participants moved to the ICU (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing IV diazepam to placebo in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizure.

10.15.4.2 Intravenous lorazepam versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more patients receiving intravenous lorazepam were seizure free compared to placebo. (HIGH QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between intravenous lorazepam and placebo for:

- incidence of hypotension, cardiac dysrhythmia or respiratory intervention (LOW QUALITY)
- proportion of participants moved to the ICU (LOW QUALITY)
- death (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to placebo in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- time to cessation of seizure.

10.15.4.3 Intravenous lorazepam versus /intravenous diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intravenous lorazepam and intravenous diazepam in achieving seizure freedom. (MODERATE QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between intravenous lorazepam and intravenous diazepam for the incidence of the following events:

- proportion of participants moved to the ICU (LOW QUALITY)
- hypotension, cardiac dysrhythmia or respiratory intervention (LOW QUALITY)
- death (LOW QUALITY).

Cost-effectiveness

No economic evidence comparing lorazepam to diazepam in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.5 Treatment of prolonged seizures and convulsive status epilepticus in children (community)

10.15.5.1 Buccal midazolam versus rectal diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

A significantly lower proportion of participants in buccal midazolam had seizure recurrence within an hour compared to participants in rectal diazepam (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between buccal midazolam and rectal diazepam for:

- the proportion of seizure-free participants (VERY LOW QUALITY)
- the proportion of participants with seizure recurrence within 24 hours (LOW QUALITY)
- the time to cessation of seizures
- the time to cessation of seizures within one hour
- the time to cessation of seizures within 24 hours

Adverse events – statistically non significant results

No significant difference between buccal midazolam and rectal diazepam for the proportion of children required intubation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing buccal midazolam to rectal diazepam in patients with status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.5.2 Intranasal midazolam versus rectal diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

A significantly lower proportion of participants in rectal diazepam were seizure free within 10 minutes compared to participants in intranasal midazolam, however there is uncertainty over the magnitude of clinical effect (VERY LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between intranasal midazolam and rectal diazepam for time to cessation of seizures. (MODERATE QUALITY)

Cost-effectiveness

No economic evidence comparing intranasal midazolam to rectal diazepam in patients with status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported:

- incidence of adverse events.

10.15.6 Treatment of acute repetitive seizures (children and adults)

10.15.6.1 Diazepam gel versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non significant results

No significant difference was found between diazepam gel and placebo for the proportion of seizure free participants. (LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants receiving diazepam gel experienced somnolence than placebo. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing diazepam gel to placebo in patients with acute repetitive seizures was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.7 Treatment of convulsive status epilepticus in adults in hospitals

10.15.7.1 Intravenous diazepam and phenytoin versus intravenous phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between intravenous diazepam with phenytoin and phenobarbital in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events - statistically non-significant results

No significant difference between intravenous diazepam with phenytoin and phenobarbital for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV diazepam and phenytoin to IV phenobarbital in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.7.2 IV Diazepam and phenytoin versus IV phenobarbital and optional phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in intravenous phenobarbital and optional phenytoin were seizure free compared to intravenous diazepam and phenytoin; however there is uncertainty in the magnitude of the clinical effect. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between intravenous diazepam with phenytoin and phenobarbital and optional phenytoin for time to cessation of seizures.

Adverse events – statistically non-significant results

No significant difference between intravenous diazepam with phenytoin and intravenous phenobarbital with optional phenytoin for the incidence of:

- hypotension (VERY LOW QUALITY)
- intubation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV diazepam and phenytoin to IV phenobarbital and optional phenytoin in patients with convulsive status epilepticus was identified.

10.15.7.3 IV Diazepam and phenytoin versus IV phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between intravenous diazepam with phenytoin and phenytoin in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between intravenous diazepam with phenytoin and phenytoin for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV diazepam and phenytoin to IV phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.7.4 IV lorazepam versus IV diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intravenous lorazepam and intravenous diazepam for the proportion of seizure free participants (after one dose of the drug). (LOW QUALITY)

No significant difference between intravenous lorazepam and intravenous diazepam for the proportion of seizure free participants (after second dose of the drug). (VERY LOW QUALITY)

No significant difference between intravenous lorazepam and intravenous diazepam for time to cessation of seizures. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to IV diazepam in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported incidence of adverse events.

10.15.7.5 IV lorazepam versus IV diazepam plus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between intravenous lorazepam and intravenous diazepam and phenytoin in achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between intravenous lorazepam and intravenous diazepam and phenytoin for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to IV diazepam and phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.7.6 IV lorazepam versus IV phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly more participants in intravenous lorazepam experienced seizure freedom compared to intravenous phenytoin, however there is uncertainty over the magnitude of its clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between intravenous lorazepam and intravenous phenytoin for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV lorazepam to IV phenytoin in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

- there were no studies that reported:
- time to cessation of seizures.

10.15.7.7 IV phenytoin versus IV Phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non- significant results

No significant difference between intravenous phenytoin and intravenous phenobarbital for the proportion of participants achieving seizure freedom. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between intravenous phenytoin and intravenous phenobarbital for the incidence of:

- hypoventilation (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV phenytoin to IV phenobarbital in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported time to cessation of seizures.

10.15.7.8 IV phenytoin versus IV sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intravenous phenytoin and intravenous sodium valproate for the proportion of seizure free participants. (LOW QUALITY)

No significant difference between intravenous phenytoin and intravenous sodium valproate for the seizure recurrence (within 12 hours). (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between intravenous phenytoin and intravenous sodium valproate for the incidence of:

- cardiac side effects (VERY LOW QUALITY)
- respiratory side effects (VERY LOW QUALITY)
- liver dysfunction (VERY LOW QUALITY)
- hypotension (VERY LOW QUALITY)
- death (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing IV phenytoin to IV sodium valproate in patients with convulsive status epilepticus was identified.

10.15.7.9 IV phenytoin versus IV fosphenytoin

Clinical evidence

No studies were identified.

Health economic evidence

Four cost-minimisation studies[347-350] comparing intravenous phenytoin to intravenous fosphenytoin were indentified in the economic literature search. All four were excluded from the health economic evidence review due to the fact that they had poor applicability and potentially serious methodological limitations. See economic evidence table in appendix M for details.

Despite the poor applicability and potentially serious limitations of these studies, they highlight important economic considerations. The studies assume that phenytoin and fosphenytoin are bioequivalent and have equivalent efficacy, therefore there should be no between-drug differences in terms of the proportion of patients achieving seizure control. Thus, differences in treatment-related costs between the drugs are likely to be driven by the time spent in the emergency department and the management of drug-related adverse events. The studies assert that fosphenytoin can be administered more rapidly and that it has a lower incidence of adverse events

than phenytoin. Consequently, cost differences based on these outcomes may favour fosphenytoin. However, without published evidence specifically comparing fosphenytoin with phenytoin in patients with convulsive status epilepticus, any extrapolation of the results conducted in other patient groups must be treated with caution.

10.15.8 Treatment of convulsive status epilepticus in children

10.15.8.1 Intranasal midazolam versus rectal/IV diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intranasal midazolam and intravenous/rectal diazepam for:

- the proportion of seizure-free participants within 10 minutes (VERY LOW QUALITY)
- the proportion of seizure-free participants within 5 minutes (MODERATE QUALITY)
- the time to cessation of seizures.

Cost-effectiveness

No economic evidence comparing buccal or intranasal midazolam to rectal or IV diazepam in children with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported an incidence of adverse events.

10.15.8.2 Intramuscular midazolam versus IV diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intramuscular midazolam and intravenous diazepam for the proportion of seizure free participants (VERY LOW QUALITY)

No significant difference between intramuscular midazolam and intravenous diazepam for the recurrence of seizures. (VERY LOW QUALITY)

No significant difference between intramuscular midazolam and intravenous diazepam for the time to cessation of seizures (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing intramuscular midazolam to IV diazepam in patients with convulsive status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported an incidence of adverse events.

10.15.8.3 Intranasal lorazepam versus intramuscular paraldehyde

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Significantly fewer participants who received intranasal lorazepam required two or more AEDs compared to participants in intramuscular paraldehyde group. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No significant difference between intranasal lorazepam and intramuscular paraldehyde for the proportion of seizure free participants. (LOW QUALITY)

No significant difference between intranasal lorazepam and intramuscular paraldehyde for the seizure recurrence within 24 hours. (VERY LOW QUALITY)

No significant difference between intranasal lorazepam and intramuscular paraldehyde for the time to cessation of seizures.

Adverse events – statistically significant results

A higher proportion of participants taking intranasal lorazepam had a drop in diastolic blood pressure by at least 5mmHg, however there is uncertainty in the magnitude of this clinical effect. (LOW QUALITY)

Adverse events – non-statistically significant results

No statistically significant difference between intranasal lorazepam and intramuscular paraldehyde for the:

- incidence of death (VERY LOW QUALITY)
- drop in systolic blood pressure by at least 5mmHg (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing intranasal lorazepam to intramuscular paraldehyde in children with convulsive status epilepticus was identified.

10.15.8.4 IV/rectal lorazepam versus IV/rectal diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between IV/rectal lorazepam and IV/rectal diazepam for the time to cessation of seizures.

Adverse events – non-statistically significant results

No statistically significant difference between IV/rectal lorazepam and Iv/rectal diazepam for the:

- incidence of respiratory depression (VERY LOW QUALITY)
- the proportion of children requiring intensive care (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV/rectal lorazepam and IV/rectal diazepam in children with convulsive status epilepticus was identified.

10.15.8.5 IV/rectal lorazepam versus IV/rectal diazepam and phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between IV/rectal lorazepam and IV/rectal diazepam and phenytoin for the proportion of seizure free participants. (MODERATE QUALITY)

No difference between intranasal IV/rectal lorazepam and IV/rectal diazepam and phenytoin for the seizure recurrence within 18 hours. (VERY LOW QUALITY)

Adverse events – non-statistically significant results

No statistically significant difference between IV/rectal lorazepam and Iv/rectal diazepam and phenytoin for the incidence of respiratory depression (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV/rectal lorazepam and IV/rectal diazepam and phenytoin in children with convulsive status epilepticus was identified.

10.15.8.6 Buccal midazolam versus IV diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Time to cessation of seizures was significantly less in children receiving IV diazepam compared to children receiving buccal midazolam. (LOW QUALITY)

Efficacy – statistically non-significant results

No significant difference between buccal midazolam and IV diazepam for the proportion of seizure free participants. (MODERATE QUALITY)

Adverse events – non-statistically significant results

No difference between intranasal buccal midazolam and IV diazepam for the incidence of the following adverse events:

- CNS depression
- respiratory depression
- apnea
- cardiac arrhythmia.

Cost-effectiveness

No economic evidence comparing buccal midazolam and IV diazepam in children with convulsive status epilepticus was identified.

10.15.8.7 Buccal midazolam versus rectal diazepam

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between buccal midazolam and rectal diazepam for the time to cessation of seizures.

Adverse events – statistically non significant results

No significant difference between buccal midazolam and rectal diazepam for the proportion of children required intubation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing buccal midazolam and rectal diazepam in children with convulsive status epilepticus was identified.

10.15.9 Treatment of refractory status epilepticus

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

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

152. If either the whole protocol or intensive care is required the tertiary service should be consulted. [2004]

153. An individual treatment pathway should be formulated for children, young people and adults who have recurrent convulsive status epilepticus. [2004]

10.15.9.1 Treatment of refractory status epilepticus in children

10.15.9.2 IV Diazepam versus sodium valproate infusion

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

Sodium valproate infusion had a significantly lower time to cessation of seizures than intravenous diazepam; however there is uncertainty over the magnitude of this clinical effect. (MODERATE QUALITY)

Efficacy – statistically non-significant results

No statistically significant difference between intravenous diazepam and sodium valproate infusion for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically significant results

Significantly more participants in the intravenous diazepam group experienced respiratory depression compared to the sodium valproate group; however there is uncertainty over the magnitude of this clinical effect. (VERY LOW QUALITY)

Significantly more participants in the intravenous diazepam group experienced hypotension compared to the sodium valproate group; however there is uncertainty over the magnitude of this clinical effect. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV diazepam to sodium valproate infusion in children with refractory status epilepticus was identified.

10.15.9.3 Midazolam infusion versus diazepam infusion

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between midazolam infusion and diazepam infusion for:

- the proportion of seizure freedom (VERY LOW QUALITY)
- time to cessation of seizures (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between midazolam infusion and diazepam infusion for the incidence of:

- hypotension (VERY LOW QUALITY)
- the number of patients requiring intubation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing midazolam infusion to diazepam infusion in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported the time to cessation of seizures.

10.15.9.4 Midazolam infusion versus IV lidocaine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No statistically significant difference between midazolam infusion and intravenous lidocaine for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No statistically significant difference between midazolam infusion and intravenous lidocaine for the incidence of:

- hypothermia (VERY LOW QUALITY)
- acidosis (VERY LOW QUALITY)
- ventilation requirement (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing midazolam infusion to IV lidocaine in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported the time to cessation of seizures.

10.15.9.5 IV Midazolam versus rectal sodium valproate

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between midazolam infusion and rectal sodium valproate for the proportion of seizure free participants. (VERY LOW QUALITY)

No significant difference between midazolam infusion and rectal sodium valproate for the time to cessation of seizures. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing IV midazolam to rectal sodium valproate in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported an incidence of adverse events.

10.15.9.6 IV Midazolam versus IV propofol

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference between intravenous midazolam infusion and intravenous propofol for the proportion of seizure free participants. (VERY LOW QUALITY)

Adverse events – statistically non-significant results

No significant difference between intravenous midazolam infusion and intravenous propofol for the incidence of:

- elevated serum creatine phosphokinase (VERY LOW QUALITY)
- serum triglyceride cholesterol (VERY LOW QUALITY)
- apnoea (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing IV midazolam to IV propofol in children with refractory status epilepticus was identified.

Outcomes with no evidence

There were no studies that reported the time to cessation of seizures.

10.15.10 New recommendations and link to evidence

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

Recommendation	**154. Give immediate emergency care and treatment to children, young people and adults who have prolonged (lasting 5 minutes or more) or repeated (three or more in an hour) convulsive seizures in the community. [2012]**
Relative values of different outcomes	Cessation of seizures is the most important outcome. All evidence has used the criterion that a prolonged seizure is one that continues for longer than 5 minutes.
Trade off between clinical benefits and harms	There is a risk of serious immediate and long term morbidity and mortality if convulsive seizure not terminated by 30 minutes and therefore treatment is required urgently.
Economic considerations	Urgent and appropriate care with consequent successful treatment delivered in the community is likely to reduce visits to A+E and subsequent hospitalisation. Early control of seizures may also reduce the mortality and morbidity risks associated with prolonged tonic-clonic seizures.
Quality of evidence	This recommendation was based on the consensus opinion of the GDG.
Other considerations	No further evidence has been published to overturn the recommendation from the previous edition of this guideline (2004). The GDG recognises that in some situations a personalised care plan may differ from the above.

Recommendation	**155. Only prescribe♦ buccal midazolam or rectal diazepam♣ for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures. [new 2012]**
Relative values of different outcomes	Cessation of seizures, adverse effects and drug tolerance are the most important outcomes. It is important that patients requiring emergency medications have access to them, but it is also important that they not be overprescribed, particularly in groups unlikely to require them.
Trade off between clinical benefits and harms	Overuse of buccal midazolam or other rescue (emergency) benzodiazepines can lead to drug tolerance and incidence of adverse events, such as sedation and respiratory suppression. The GDG considered that over- and potentially inappropriate prescription of emergency benzodiazepines should not be used as a means to alleviate individual, parental or carer's anxiety.
Economic considerations	No economic evidence was available to inform the GDG on the relative cost-effectiveness of selective or general prescribing of emergency benzodiazepines. However, the GDG considered it important to direct clinicians to more appropriate and more selective prescribing of these emergency medications as they can be very costly and carry serious risks if administered incorrectly. Targeting their usage in the community to those patients with a known risk of prolonged or repeated convulsive seizures has the potential to save NHS resources both in terms of the medications themselves and in terms of avoiding hospitalisation due to inappropriate administration.
Quality of evidence	There was no clinical evidence. This recommendation was based on consensus opinion of the GDG.
Other considerations	There may be access and equality issues arising from the exclusion of children in need of emergency benzodiazepines from normal activities due to a lack of trained personnel.

♦ In line with normal standards in emergency care.

♣ At the time of publication (Janaury 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**156. Administer buccal midazolam as♦ first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Administer rectal diazepam♣ if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam. [new 2012]**
Relative values of different outcomes	Cessation of seizures was considered the most important outcome. Ease and acceptability of administration of buccal midazolam is also important.
Trade off between clinical benefits and harms	Buccal midazolam is more effective and more dignified and socially acceptable than rectal diazepam. The advantage of lorazepam over diazepam lies on the pharmacokinetics and its longer half life; however IV lorazapam is only appropriate in situations where IV access is established and resuscitation facilities are available. The risks of potential side effects of these drugs are outweighed by the need to stop seizures rapidly
Economic considerations	No economic evidence was available to inform the GDG on the relative cost-effectiveness of buccal midazolam, rectal diazepam and IV lorazepam. Acquisition costs of buccal midazolam are greater than rectal diazepam, but the clinical evidence shows it to be more effective in terms of controlling seizures, preventing recurrence of seizures and requiring fewer additional rescue or emergency drugs to treat the initial episode. In addition to being more effective, buccal midazolam also has practical advantages compared to rectal diazepam because the buccal route provides a simpler and more dignified method of administration. Delays to effective administration of treatment at this acute stage can have a very important impact on subsequent costs and outcomes for this group of patients.
Quality of evidence	In adults, the quality of evidence use was moderate as it was a double blinded study with good randomization and allocation concealment. This study included intravenous route of administration but was delivered by paramedics out of hospital. In children, three RCTs were included; two double blinded and one unblinded. There were different routes of drug administration between studies.
Other considerations	None

♦ In line with normal standards in emergency care

♣ At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

Recommendation	**157. Depending on response to treatment, the person's situation and any personalised care plan, call an ambulance, particularly if:** • **the seizure is continuing 5 minutes after the emergency medication has been administered** • **the person has a history of frequent episodes of serial seizures or has convulsive status epilepticus, or this is the first episode requiring emergency treatment or** • **there are concerns or difficulties monitoring the person's airway, breathing, circulation or other vital signs. [new 2012]**
Relative values of different outcomes	Rapid cessation of seizures is the most important outcome. All evidence has used the criterion that a prolonged seizure is that continuing beyond 5 minutes.
Trade off between clinical benefits and harms	There is a risk of serious immediate and long term morbidity and mortality if a convulsive seizure not terminated by 30 minutes. Therefore the aim should be for individual to reach hospital before this duration has passed. There is an unknown risk of side effects on first time administration of emergency medication and a possibility that further seizures will require treatment with intravenous medication
Economic considerations	Prompt and effective treatment of prolonged and repeated seizures is likely to lead to less and shorter duration of hospitalisation.
Quality of evidence	There is no clinical evidence. This recommendation was based on the consensus opinion of the GDG.
Other considerations	This recommendation is a modification of one in the first edition of this guideline (2004), as the view of the GDG was that further clarification was required as part of the management of convulsive status epilepticus.

Treatment for children, young people and adults with convulsive status epilepticus in hospital

Recommendation	**158. For children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus) who are in hospital, immediately:** • **secure airway** • **give high-concentration oxygen** • **assess cardiac and respiratory function** • **check blood glucose levels and** • **secure intravenous access in a large vein.** **See also the suggested protocols in appendix K. [new 2012]**
Relative values of different outcomes	Status epilepticus should be regarded as a medical emergency and consequently basic resuscitation guidelines for initial treatment should be followed. Further, hypoglycaemia should be excluded as a cause of a generalised tonic clonic seizure.
Trade off between clinical benefits and harms	Basic resuscitative procedures should not delay the treatment targeted at cessation of the seizures.
Economic considerations	No economic data was available to inform on the relative cost effectiveness of emergency measures. However basic resuscitative procedures are recommended to reduce intensive care admission and longer term morbidity.
Quality of evidence	This recommendation was based on the consensus opinion of the GDG.
Other considerations	Modified recommendation from original guideline (GPP), as the view of the GDG was that further clarification was required as part of the management of convulsive status epilepticus.

Recommendation	**159. Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). Administer intravenous diazepam if intravenous lorazepam is unavailable, or use buccal midazolam if unable to secure immediate intravenous access. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment). See also the suggested protocols in appendix K. [new 2012]**
Relative values of different outcomes	Cessation of seizures was considered the most important outcome.
Trade off between clinical benefits and harms	The benefits outweigh harms for the use of IV lorazepam. The advantage of lorazepam over other AEDs lies in its pharmacokinetics as it tends to work quickly and for a longer time (longer half life) and consequently patients need fewer additional rescue drugs. However there have been issues with the availability of lorazepam and in this instance the GDG opinion was that intravenous diazepam would be a suitable alternative. There was no significant difference found between intravenous lorazepam and intravenous diazepam in the evidence.
Economic considerations	No economic evidence was available to inform the GDG on the relative cost-effectiveness of different emergency AEDs used to treat patients with status epilepticus once they have reached hospital. At current price, lorazepam is an inexpensive drug (£0.35 per 4 mg dose) and the evidence showed it to be effective compared to a range of other drugs (diazepam, paraldehyde, phenytoin). Midazolam was shown to be effective in the community setting, and its greater effectiveness over diazepam almost reached statistical significance in the hospital setting. Its greater cost compared to lorazepam may be justified if more immediate access is required.
Quality of evidence	The evidence for this recommendation was retrieved from two double blinded RCTs of poor quality, without information on randomization and allocation concealment.
Other considerations	Due to the potential risk of respiratory compromise associated with the use of benzodiazepines, facilities for supporting respiratory depression or failure should be immediately available. No further published evidence overturns the original recommendation.

Recommendation	**160. If seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). See also the suggested protocols in appendix K. [new 2012]**
Relative values of different outcomes	Cessation of seizures was considered to be the most important outcome.
Trade off between clinical benefits and harms	Phenytoin with benzodiazepines was equally effective as phenobarbital. Both emergency AEDS are equal in terms of adverse events.
Economic considerations	No economic evidence was available to inform the GDG on the relative cost-effectiveness of different emergency AEDs used to treat patients with convulsive status epilepticus once they have reached hospital. The GDG considered that the unit cost of iv phenobarbital, phenytoin or sodium valproate was broadly similar and that each have similar efficacy profiles. Electrocardiographic (ECG) and blood pressure monitoring must accompany the intravenous administration of phenytoin.
Quality of evidence	The quality of evidence for this recommendation was moderate to poor; one study was double blinded study with no allocation concealment and three studies were unblinded with partial or no allocation concealment.
Other considerations	No other considerations.

Refractory convulsive status epilepticus

Recommendation	**161. Follow the suggested protocols in appendix K for treating refractory convulsive status epilepticus in secondary care. [2012]**
Relative values of different outcomes	Not applicable.
Trade off between clinical benefits and harms	Status epilepticus is a medical emergency and must be treated as soon as possible to stop the seizures in order to avoid brain damage and in some cases death. Refractory convulsive status epilepticus is where seizures have not been controlled with initial treatment, therefore the need to stop the seizures is very urgent.
Economic considerations	Not applicable.
Quality of evidence	This recommendation was based on GDG consensus. The children's protocol was produced by the British Paediatric Neurology Association and the adults protocol was compiled by the first epilepsy guideline development group in 2004. The adult's protocol has further been updated by the current epilepsy guideline development group.
Other considerations	The GDG considered the need for emergency protocols to be in place to ensure patients receive the correct medication to stop the seizures as quickly as possible.

Recommendation	**162. Administer intravenous midazolam*, propofol* or thiopental sodium* to treat♦ adults with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and critical life systems support are required. See also the suggested protocols in appendix K. [new 2012]**
Relative values of different outcomes	The GDG considered cessation of seizures and time to cessation of seizures as the most important outcomes.
Trade off between clinical benefits and harms	Use of thiopental sodium requires adequate critical care support with continuous (or at least daily) EEG monitoring to ensure seizure cessation. Continual review required of duration of treatment vers usseizure cessation with propofol or thiopental.
Economic considerations	No economic data was available to inform cost effectiveness of treatment. Shorter duration of status epilepticus likely to reduce long term intensive care admission and long term sequelae.
Quality of evidence	No RCT evidence was found for adult refractory population. The recommendation on propofol and thiopental was based on GDG expertise and the recommendation on midazolam was based on evidence derived from children population.
Other considerations	The GDG stated that no further published evidence overturns the original recommendation.

* At the time of publication (Janaury 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

♦ In line with normal standards in emergency care.

Recommendation	**163. Administer intravenous midazolam♣ or thiopental sodium♣ to treat children and young people with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and critical life systems support are required. See also the suggested protocols in appendix K. [2012]**
Relative values of different outcomes	The GDG considered cessation of seizures and time to cessation of seizures as the most important outcome.
Trade off between clinical benefits and harms	Use of thiopental sodium requires adequate critical care support with continuous (or at least daily) EEG monitoring to ensure seizure cessation. Continual review required of duration of treatment vs seizure cessation. Propofol not recommended for treatment of status epilepticus in children.
Economic considerations	No economic data was available to inform cost effectiveness of treatment. Shorter duration of status epilepticus likely to reduce long term intensive care admission and long term sequelae.
Quality of evidence	The recommendation of midazolam was retrieved from 5 un-blinded RCTs of poor quality. The recommendation of thiopental was based on GDG expertise and consensus, including British Paediatric Neurology Association prepared guidelines (appendix C)
Other considerations	The GDG stated that no further published evidence overturns the original recommendation.

10.15.11 New research recommendations (for full list see section 2.11)

10.15.11.1 Treatment of convulsive status epilepticus (i.e. not just refractory)

What is the most effective and safest anticonvulsant to treat:

a. established (usually lasting longer than 30 minutes) convulsive status epilepticus

b. refractory convulsive status epilepticus

Why is this important?

Convulsive status epilepticus (CSE) should be treated as an emergency. The most important aspect of treatment is to try to stop the seizure. Prompt, successful treatment of CSE avoids the need for admission to an intensive care unit (ICU). The most commonly used medication is phenytoin. This should be used with care and close monitoring because of the risk of hypotension and cardiac arrhythmia. Sodium valproate and levetiracetam are potentially as effective and safer alternatives but there are very limited comparative data.

CSE that is refractory to first-line treatment (RCSE) is rare and often complicated by irreversible neurological and intellectual sequelae, including death. Reasons for these complications include the underlying cause of RCSE, its duration and management. The majority, if not all patients with RCSE

♣ At the time of publication (Janaury 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix K for details). Informed consent should be obtained and documented.

are managed in an ICU. There are no agreed drugs or treatment protocols for treating RCSE. The three most commonly used anticonvulsants are thiopental sodium, midazolam and propofol (propofol is rarely used in children). Data on treatment in children, young people and adults are limited and anecdotal. A recently completed 2-year audit of everyone younger than 16 years with RCSE treated in an ICU in England, Wales and Scotland will provide unique epidemiological data on paediatric RCSE, its causes and current management. These data could be used to design a randomised controlled trial (RCT) of specific drug treatments and protocols.

The research should include

- a multicentre randomised comparative trial of intravenous levetiracetam, sodium valproate and phenytoin in initial treatment of status epilepticus
- a multicentre RCT of treatment of refractory status epilepticus in ICUs, including midazolam and thiopental sodium (and propofol in adults)
- primary outcome of cessation of CSE
- secondary outcomes including recurrence within a designated period (probably 12 hours), mortality and morbidity
- cost data including treatment costs and days in intensive care.

10.16 Non-convulsive status epilepticus

164. Non-convulsive status epilepticus is uncommon and management is less urgent. A suggested guideline can be found in appendix K. [2004]

10.16.1 Introduction

Non-convulsive status epilepticus is an under-diagnosed syndrome whereby clinically subtle seizures result in a depressed level of consciousness. Non-convulsive status epilepticus is divided into two main subgroups: generalised non-convulsive status and focal status.Nonconvulsive status epilepticus is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms including change in behavior and or awarenesss.Subtle generalised convulsive status was defined in the study conducted by Treiman et al [336]as the stage of generalised convulsive status when the patient is in continuous coma but only subtle motor convulsions are seen. Tomson et al [351] defined non-convulsive status epilepticus as a state of impaired consciousness or responsiveness without convulsions lasting at least 60 minutes.

For this clinical question, we additionally searched for any observational studies as it was initially thought that no randomised evidence on non-convulsive status epilepticus was available.

The BNF states that: the urgency to treat non-convulsive status epilepticus depends upon the severity of the patient's condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

10.16.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

No RCTs (blinded or un-blinded) were found for this evidence review so observational studies were included as a study design providing lower quality of evidence.

For this review we included adults and children with non-convulsive status epilepticus. The only outcome measures included in this review were: the proportion of participants whose seizure was stopped (seizure free), duration of time to cessation of seizure, and incidence of adverse events.

10.16.3 AEDs for the treatment of non-convulsive Status Epilepticus (observational study)

10.16.3.1 IV diazepam versus IV clonazepam

Clinical evidence

Thirty two patients with non-convulsive status epilepticus were diagnosed at the department of Neurology at the Soder Hospital in Sweden, as part of a prospective study carried out by Tomson et al1. Non-convulsive status epilepticus was defined as a state of impaired consciousness or responsiveness without convulsions lasting at least 60 minutes. An ictal EEG showing continuous or almost continuous seizure activity was required for inclusion. The median age at onset was 51 years. Ten patients had status as their first epileptic manifestation, but most patients had a previous history of epilepsy. The median duration of epilepsy at onset of status was 4 years.

Three patients recovered spontaneously from status during EEG recording. Twenty-five patients were treated with IV diazepam (5-10mg), 3 patients were treated with clonazepam (1mg), and 1 with both. The effect on EEG and clinical state was immediate and lasting in 10 patients and immediate but followed by recurrence of the status within hours in 18 patients. In 1, no immediate effect was evidence. In 8 patients, as lasting effect was not achieved until IV phenytoin (250-500mg) was added.

Health economic evidence

No studies were identified in the economic literature search.

10.16.4 New recommendations and link to evidence

No new recommendations were developed.

10.16.5 Generic prescribing

This was not a key clinical question, and therefore no evidence review was undertaken. This is an important issue in the prescribing of AEDs, and prescriber is advised to consult the BNF for specific advice for different AEDS. For example, for carbamazepine, the BNF states that 'different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation'; for phenytoin, that 'on the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'.[352]

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

10.17.1 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.[353]

165. All children, young people and adults with epilepsy should have access via their specialist to a tertiary service when circumstances require. [2004]

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

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

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

169. If seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, children, young people and adults should be referred to tertiary services soon[ee] for further assessment. Referral should be considered when one or more of the following criteria are present:

- **the epilepsy is not controlled with medication within 2 years**
- **management is unsuccessful after two drugs**
- **the child is aged under 2 years**
- **a child, young person or adult experiences, or is at risk of, unacceptable side effects from medication**
- **there is a unilateral structural lesion**
- **there is psychological and/or psychiatric co-morbidity**
- **there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome. [2004]**

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

171. Behavioural or developmental regression or inability to identify the epilepsy syndrome in a child, young person or adult should result in immediate referral to tertiary services. [2004]

172. Children, young people and adults with specific syndromes such as Sturge–Weber syndrome, the hemispheric syndromes, Rasmussen's encephalitis and hypothalamic hamartoma should be referred to a tertiary epilepsy service. [2004]

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

Evidence statement

[ee] The Guideline Development Group considered that 'soon' meant being seen within 4 weeks.
[ff] In this recommendation, 'centre' has been replaced with 'service' for consistency across the recommendations.

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 1999[354]

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.'[354]

Wiebe 2001[355]

This RCT assessed the efficacy and safety of surgery in adults with poorly controlled temporal lobe epilepsy.

Eighty participants were randomly assigned to either surgery (n=40) or treatment with AEDs for 12 months (n=40). The primary outcome was freedom from seizures that impaired awareness of self and surroundings. The analysis was done on an intention-to-treat basis.

Of the 36 who underwent surgery, 58% were free from seizures that impaired awareness at 12 months, compared with 8% in the medical group ($p<0.001$). 38% of those in the surgical group compared with 3% in the medical group were seizure free, including auras, at 12 months ($p<0.001$).

One individual died of SUDEP in the medical group. No deaths occurred in the surgical group.

The authors suggested that this trial supported the belief that prolonged trials of medication were futile and that people with temporal lobe epilepsy should be evaluated for surgery. However, they stress that the question of whether early surgery was superior to medical therapy was not addressed.

Health economics

Clinical research has shown that surgery is a desirable option for treatment of certain forms of refractory epilepsy. There is a lack of health economics evidence in the assessment of surgery in the management of epilepsy. One review with economic analysis and one economic evaluation on epilepsy surgery were found. However, no randomised controlled trial alongside an economic evaluation was found.

Chilcott and colleagues 1999[354]

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' heath authority, between 3 and 14 surgical candidates would be identified per year. The cost per person going forward to surgery for assessment was estimated between £10k and £16k. The total cost per year for assessment and surgery for a healthy authority was estimated between £60k and £220k.

- The average cost per person per year of active epilepsy (at least one seizure in the last year) is £530 compared to £75 for inactive epilepsy.
- Surgery results in approximately 65% of individuals undergoing temporal lobe resection (TLR) and 45% of individuals undergoing extra temporal resection (ETR) becoming seizure free. 10% of those on medical management become seizure free.
- The base case model marginal cost per seizure free year compared to medical management is £2291 for TLR individuals, £4,096 for ETR individuals and £2,329 for all surgical cases.

The results were particularly sensitive to the time horizon used in the analysis.

Key parameters were the effectiveness of surgery and the proportion of those who proceed to surgery from neuropsychological testing.

The authors recognised that there was a lack of trial data, a likely referral bias in case series from the major centres, differences in practice between trial centres. The review also states that a NHI consensus statement recognised that there was a lack of evidence linking seizure control to quality of life and identified this as an area for research. For these reasons, the review should be viewed with caution.

11 The role of non-drug treatments in the management of the epilepsies

11.1 Introduction

Although the mainstay of treatment for individuals with epilepsy is pharmacological, non-drug treatments such as psychological interventions, the ketogenic diet and vagus nerve stimulation are also used.

Psychological interventions such as relaxation therapy, cognitive behaviour therapy and 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 (KD) is a high-fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation when ketone bodies become the main fuel for the brain's energy demands (Hartman 2008) [356]. It has long been used for treatment of refractory epilepsy in children, although the exact mechanism of action is unclear.

It can be difficult to treat individuals with drug resistant epilepsy who have been assessed as being unsuitable for surgery. Vagus nerve stimulation (VNS) is a further adjunctive treatment that may be considered in such cases.

11.2 Does the treatment of epilepsy in adults or children with psychological methods lead to a reduction in seizure frequency and/or a better quality of life?

174. Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]

175. Psychological interventions (relaxation, cognitive behaviour therapy, biofeedback) may be used in conjunction with AED therapy in adults where either the person 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 people. [2004]

176. Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children and young people with drug-resistant focal epilepsy. [2004]

11.3 Ketogenic Diet

11.3.1 Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation when ketone bodies become the main fuel for the brain's energy demands (Hartman 2008)[356]. It has long been used in the treatment of refractory epilepsy in children, although the exact mechanism of action is unclear.

The KD diet was initially reported for use in epilepsy in 1921 (Wilder 1921)[357]. The initial diet used was the classical ketogenic diet, based on the ratio of fat to carbohydrate (with protein), of 3 or 4:1. Later an alternative was suggested using triglyceride oil as a supplement, the Medium Chain Triglyceride (MCT) Diet (Huttenlocher et al 1971)[358]. These diets have to be carefully administered with the aid of a dietician.

In this chapter we examine the effectiveness, adverse effects and cost effectiveness of ketogenic diets compared to no change in diet (placebo) and to no diet (normal diet) in the treatment of childhood epilepsy. There have been two randomised controlled trials examining efficacy. One very small trial compared the ketogenic diet against placebo. The other trial compared the ketogenic diet (classical or MCT variant) with a control group (normal diet). Additional data from this second comparison included an analysis on the relative efficacy and tolerability between the classical and the MCT ketogentic diets.

11.3.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included adults and children with epilepsy. No randomised data was found for adults.

11.3.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different variants of the ketogenic diet and no change in diet. The following interventions were included in our search; ketogenic diet, ketogenic diet plus glucose, Medium Chain Triglycerides Diet (MCT) and modified-Atkins diet. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found, and in this case, no section on this comparison is included in the chapter.

Normal diet (without dietetic input)			
Ketogenic diet	1 [359]		
Ketogenic diet plus glucose		1 [360]	

MCT ketogenic diet		1 [361]		
	Normal diet (without dietetic input)	Ketogenic diet	Ketogenic diet plus glucose	MCT ketogenic diet

11.3.3.1 Ketogenic Diet versus no change in treatment (without dietetic input)

Clinical evidence

For details of the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically significant results

The ketogenic diet is more effective than no change in treatment in the proportion of participants experiencing at least 50% reduction in seizures. However, there is uncertainty about the magnitude of the effect. (LOW QUALITY)

Efficacy – statistically non significant results

No significant difference between the ketogenic diet and the no change in treatment in the proportion of participants achieving seizure freedom (VERY LOW QUALITY)

Adverse events- statistically significant results

The ketogenic diet has significantly greater incidence of the following adverse events compared to no change in treatment, however there is uncertainty of the magnitude of the clinical effect:

- vomiting (LOW QUALITY)
- constipation (LOW QUALITY)
- medication needed for constipation (LOW QUALITY)
- lack of energy(LOW QUALITY)
- hunger. (LOW QUALITY)

Cost-effectiveness

No economic evidence comparing the ketogenic diet to no change in treatment was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

11.3.3.2 Ketogenic Diet versus ketogenic diet plus glucose

The authors of the trials believe that using a 60g solution of glucose over the course of a day in conjunction with a ketogenic diet negates urinary and serum ketosis creating a placebo arm. The use of an artificial sweetener (saccharin, which tastes similar to glucose) does not add carbohydrate and therefore was used in the treatment arm. Ketosis was never lost by patients in the glucose arm.

Clinical evidence

For details of the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between the ketogenic diet and placebo in the proportion of participants experiencing at least 50% reduction in seizure frequency. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing the ketogenic diet to placebo was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- incidence of adverse events,
- cognitive outcomes
- quality of life outcomes.

11.3.3.3 Classical ketogenic diet versus Medium- Chain Triglycerides ketogenic diet (MCT)

The classical ketogenic diet is based on a ratio of 4:1 or 3:1 fat to carbohydrate and protein. The fat component is provided by long-chain fat. For the MCT ketogenic diet, medium-chain triglycerides are used as an alternative fat source. MCT yields more ketones per kilocalorie than the classical ketogenic diet. It is absorbed more efficiently and is carried directly to the liver in the portal blood, thus less fat is needed and so in theory more carbohydrate and protein can be included in the diet.

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economic evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between the classical ketogenic diet and MCT ketogenic diet for the proportion of participants experiencing at least a 50% reduction in seizure frequency at 12 months. (VERY LOW QUALITY)

Adverse events – statistically non-significant

There was no significant difference between the classical ketogenic diet and the MCT ketogenic diet for the incidence of:

- vomiting (VERY LOW QUALITY)
- constipation (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing the classical ketogenic diet to the MCT ketogenic diet was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- withdrawal due to adverse events
- withdrawal due to lack of efficacy
- time to first seizure,
- time to exit/withdrawal of allocated treatment
- time to 12-month remission
- cognitive outcomes
- quality of life outcomes.

11.3.4 New recommendations and link to evidence

Recommendation	***177.* Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet. [new 2012]**
Relative values of different outcomes	GDG considered efficacy based on 50% seizure reduction and adverse effects to be the most important outcomes.
Trade off between clinical benefits and harms	One study showed that more children achieved at least a 50% reduction in seizure frequency on the ketogenic diet than no change in treatment. However, another smaller study showed that there was no significant difference in effect between the ketogenic diet and placebo. The GDG placed less weight on this smaller study, as it was not powered sufficiently to demonstrate any difference. Although the ketogenic diet was considered more effective, the evidence did not support a recommendation for any specific variant of the ketogenic diet. Any benefit may be mitigated by the frequency of side-effects and difficulty in complying with the diet. The diet may be associated with significant gastro-intestinal side-effects, including diarrhoea, constipation, vomiting and hunger. Side effects can be improved by dietary manipulation and may improve spontaneously after a few weeks. Compliance with, and adherence to, the diet is generally more difficult than compliance with antiepileptic medication. This is largely because the diet is unnatural, involves a complete change of eating habits, and frequently life-style, and this involves the whole family as well as the child. Compliance with the diet must be complete and consistent to optimise its efficacy. According to GDG experience, a successful and sustained response to the ketogenic diet can allow for the successful withdrawal of some or all concomitant AEDs in some patients, which may lead to a reduction in side effects experienced. Successful withdrawal of these drugs may not translate to overall cost savings due to the high costs of diet initiation and follow-up.
Economic considerations	The GDG recognised that implementation of the ketogenic diet would represent an additional cost compared with no dietary change, but based on the clinical evidence would also reduce seizure frequency for some patients. In the absence of a full economic evaluation to assess the potential cost-effectiveness of the ketogenic diet, the GDG considered some of the substantial costs of implementing the diet, particularly those related to initiation and follow-up. Initiation of the diet requires substantial dietetic input in terms of teaching families about the diet, following up and making adjustments during the first several weeks and months and liaising with other health professionals involved in the child's care. GDG members with experience of administering the ketogenic diet estimated that in terms of a dietician's time, initiating the diet would require roughly eight

	hours to set up and two hours per week of follow-up for the first several months. According to the PSSRU[362], the hourly rate for dietician time is between £23 and £30, which means that the first three months of treatment, including initiation, would cost between £780 and £1,020 per patient. Because of this high initial cost, it is essential that a thorough assessment be made prior to diet initiation to identify those patients for whom the diet is a suitable treatment option. The diet will most often be initiated as an outpatient, but there are some patients who will require initiation as an inpatient. The majority of costs associated with the ketogenic diet come from initiation and follow-up within the first year, although ongoing costs will include regular contact with the ketogenic diet clinic staff to monitor and manipulate the diet, ensure dietary supplementation (vitamins, minerals and KetoCal) and regular blood tests. Following the initial three months this would amount to approximately one hour per month of dietician time for as long as the child is on the diet. The clinical and blood test-monitoring will be greater than that required for children taking anti-epileptic medication. It is possible that the longer the diet is successfully maintained, achieving the desired response, the more cost-effective it may be. The GDG considered that because of the high initial costs and the potential difficulty in implementation of and adherence to the diet, it should be reserved for those children who have previously tried other AEDs but failed to achieve the desired level of seizure control. Based on the clinical evidence, the MCT ketogenic diet was not clearly more effective than the classical ketogenic diet, yet the cost of administering it is greater due to the additional cost of Liquigen (£2.90 per 100mL). In the absence of evidence to indicate greater effect, the GDG felt that the classical ketogenic diet should be tried first and the MCT ketogenic diet should be reserved for those patients with special considerations, such as older children or those who are unable to cope with or tolerate the classical variant.
Quality of evidence	Very limited trial data. The evidence is mostly of low quality. There are a limited number of events and very wide confidence intervals.
Other considerations	There is currently variation in access to ketogenic diet across England and Wales which will be important when implementing this recommendation.

11.3.5 New research recommendations (for full list see section 2.11)

11.3.6 Ketogenic diet in adults

What is the effectiveness and tolerability of the ketogenic diet in adults with epilepsy?

Why is this important?

There are no data on the use of the ketogenic diet in adults. This may reflect the fact that the diet has been shown to be ineffective and the results unpublished, or, as is more likely, that the diet has never been used in this age group. In view of the numerous anecdotal and randomised controlled data demonstrating its effectiveness and that the number of antiepileptic drugs prescribed may be reduced as a result of this dietary approach in the paediatric epilepsies, it is appropriate to undertake a randomised controlled trial of ketogenic diet in adult patients with drug-resistant epilepsy.

The research should include:

- an initial pilot study of the feasibility and acceptability of the ketogenic diet in adults who are independent in activities of daily living and who have no learning difficulties
- if the pilot study indicates that the ketogenic diet is feasible and acceptable, a multi-centre randomised controlled study should be designed; this could evaluate one or more variants of the diet versus a normal diet
- primary outcome would be reduction in seizure-frequency
- secondary outcomes would include quality of life and reduction of antiepileptic drug burden
- cost data should include the total cost of the diet (including dietetic support), reduced drug costs and reduced admissions

11.4 In people with drug resistant epilepsy, is vagus nerve stimulation (VNS) effective as an adjunctive treatment?

178. 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 focal seizures[♣] (with or without secondary generalisation) or generalised seizures. [2004, amended 2012]

179. Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures[♣] (with or without secondary generalisation) or generalised seizures[*]. [2004, amended 2012]

Evidence statement

[♣] In this recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.

[*] Evidence from 'Vagus nerve stimulation for refractory epilepsy in children', NICE interventional procedure guidance 50 (2004).

The evidence shows that VNS appears to be an effective and well tolerated treatment for drug resistant focal seizures. Stimulation using the high stimulation paradigm is significantly better than low stimulation. (Ia)

Details

Secondary Evidence

One Cochrane review [363] and one technology appraisal[364] were identified that addressed the use of VNS in the management of focal seizures and drug resistant epilepsy respectively.

In addition, guidance on the use of VNS as an interventional procedure in children[365] was published by NICE in 2004. The guidance is included in the guideline recommendations above.

Privitera 2003[363]

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 focal 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[366,367] were parallel trials, sponsored by Cyberonics as part of their pre-approval program for VNS. Each trial tested two stimulation paradigms for VNS. All participants were implanted with a stimulator, but the control group received less frequent and lower intensity stimulation. In addition, participants in the control group did not receive any electrical current when the device was activated by the hand-held magnet. A total of 312 individuals were randomised to treatment.

Stimulation parameters in the E03 trial[366] were: current 0.5 to 3.0 mA (active and control); frequency 20 to 50 Hz (control 1 to 2); pulse width 500 (control 130); on time 30 to 90 seconds (control 30 seconds); off time 5 minutes (control 90 minutes).

Stimulation parameters in the E05 trial[367] 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 focal seizures, VNS appeared to be an effective and well tolerated treatment.[363]

Bryant 1998[368]

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 2001[364]

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 upated a previous TechNote published in 1998. Corabian and Legget found:

- No published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of generalized epilepsy;
- No published prospective controlled trials or other comparative studies using controls conducted to evaluate the safety and efficacy of VNS therapy for treatment of specific types of epilepsy in children;
- No results obtained from prospective controlled studies or other comparative studies using controls that have been published on the direct comparison between the use of VNS and the use of new AEDs as adjunctive therapies for seizure frequency reduction in refractory epilepsy; and
- No prospective controlled studies or other comparative studies with controls designed and conducted to determine the effect of VNS on seizure control in refractory epilepsy in terms of reduced seizure intensity/duration and AED intake in individuals with refractory epilepsy or improved QOL.

However, the authors did review several uncontrolled trials. They concluded that VNS was safe and effective when added to the existing treatment regimen for some individuals (aged over 12 years) in terms of a reduction in seizure frequency.

Raeburn 2003[369]

The cost utility of VNS in medically refractory epilepsy was estimated based on a meta-analysis of two RCTs. However, one of the publications used reported preliminary results from a trial published in full later. This meta-analysis was therefore excluded.

Fisher 1999[370]

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.[363]

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 focal seizures who are not candidates for potentially curative surgical resections.

Primary evidence

No RCTs were identified as being published since the HTA (2000 onwards).

Health economics

Bryant 1998[368]

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 1999[371]

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.[371]

12 Information needs of individuals, families, and carers

12.1 Introduction

Having a first seizure is a very traumatic and worrying event for the individual and their family and/or carers. If epilepsy is diagnosed, then the diagnosis can have wide ranging physical and psychological and social consequences which may be as difficult to deal with as the seizures themselves. The management of epilepsy in individuals may require long–term drug treatment and regular review of their condition is essential.

It is therefore crucial that appropriate information and support for the individual with epilepsy and their family and/or carers is provided at each stage of the care pathway. Individuals with epilepsy, their families, and professionals involved in their care need information appropriate to the individual's developmental age, gender, culture, and stage of life. Potential positive outcomes of information giving and support include reduced mortality and morbidity, individual empowerment and the means to make informed decisions to achieve the best possible quality of life.

12.2 Information needs of the individual with epilepsy, the family, the carer, and special groups

180. Children, young people and adults with epilepsy and their families and/or carers should be given, and have access to sources of, information about (where appropriate):

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

- **voluntary organisations, such as support groups and charitable organisations, and how to contact them. [2004]**

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

182. Information should be provided in formats, languages and ways that are suited to the child, young person or adult's requirements. Consideration should be given to developmental age, gender, culture and stage of life of the person. [2004]

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

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

185. Checklists should be used to remind children, young people and adults, and healthcare professionals, about information that should be discussed during consultations. [2004]

186. Everyone providing care or treatment for children, young people and adults with epilepsy should be able to provide essential information. [2004]

187. The child, young person or adult 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 child, young person or adult and/or their family and/or carers are met. [2004]

Evidence statements

- Individuals with epilepsy require information on:
- epilepsy in general
- diagnosis and treatment options
- medication and side effects
- seizure type(s), triggers and obtaining optimal seizure control
- prognosis
- safety, risk and injury prevention
- psychological issues (especially stress)
- social security benefits, driving regulations and insurance
- employment; life style and social issues. (III)
- Counselling issues are anxiety, depression, emotional support and information. (III)
- People with epilepsy prefer verbal and written information that is personally relevant. (III)

Details

There is extensive literature on the general information needs of the individual with epilepsy and their families or carers.

It was agreed with the individual patient representatives on the GDG that the recommendations on information needs should be mapped to key points on the care pathway rather than summarised in a separate section of the guideline.

As far as the evidence base is concerned the focus was on published studies that reported the information needs of people with epilepsy and their families or carers. Published studies that have surveyed or interviewed people with epilepsy and/or their carers/family and reported specifically on information needs were included. Evidence that reported healthcare professionals' views as to what individuals' information needs are and studies looking more generally at the experience of adults and children living with epilepsy were excluded.

In 2001, Lynette Couldridge and colleagues published a systematic review[372] on the information and counselling needs of people with epilepsy. All the papers referenced in the Couldridge review were reviewed, and a similar strategy was used to identify any relevant papers published since. The knowledge and experience of the GDG were used to help in the identification of 'grey literature' and surveys that contributed to the evidence base.

In this review the findings of the Couldridge review[372] were presented with research identifying specific information needs at specific points on the care pathway was summarised.

Secondary evidence

Couldridge 2001[372]

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.[373]
- 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.

12.3 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.

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

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

Evidence statement

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

Details

McNelis 1998[374]

The Child Report of Psychosocial Care Scale was used to measure children's satisfaction with healthcare received, need for information and support and seizure-related concerns and fears in children with new-onset seizures. The sample of 63 children (33 girls and 30 boys), 8-14 years, completed the scale two times, 3 months and 6 months after their first seizure. Results indicated that children wanted information related to the seizure condition, especially managing their condition, and support, in the form of talking to other children with seizures.

Investigations

This should relate to initial outpatient appointment with the appropriate specialist/epilepsy specialist nurse and any subsequent follow up appointments.

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

Evidence statement

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

Details

Dilorio 1993[375]

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.[375]

Although this study did not relate the learning need to timing, both the results of tests and the reasons for such tests were ranked higher by individuals than by healthcare providers, and it could be argued that this information would be best provided when tests are ordered/ performed and results are discussed.

Ridsdale 2002[376]

A UK RCT of a nurse intervention recruited 90 adults with newly diagnosed epilepsy (mean age 40 years, range 17 to 83 years). A sub group of 31 individuals were identified for interview in the qualitative arm of the trial, 24 agreed to participate. Some found a diagnosis of epilepsy when test results were normal confusing.

Diagnosis

This should relate to initial outpatient appointment with specialist / epilepsy specialist nurse and any subsequent appointments as appropriate.

191. Children, young people and adults with epilepsy should be given appropriate information before they make important decisions (for example, regarding pregnancy or employment). [2004]

192. Children, young people and adults and their families and/or carers should be given an opportunity to discuss the diagnosis with an appropriate healthcare professional. [2004]

Evidence statements

Adults want the diagnosis to be confirmed and counselling to be available. (III)

Adults want basic information on epilepsy (what it is, causes, how common it is etc.) and some want more extensive information (education, employment, leisure, benefits, social implications etc). (III)

Younger and middle aged people want information on epilepsy and driving. (III)

Older people with epilepsy want to learn about their new condition in addition to managing current ones, including the complications of adding new drugs to the current regime. (III)

There is a need for information to be given to carers to enable them to help the individual with epilepsy manage their condition, as well as to intervene effectively when they are unable to help themselves. (III)

Bereaved relatives would like information on epilepsy to be provided automatically to the individual with epilepsy either on or soon after diagnosis. (III)

Individuals with epilepsy and their families should be informed about the risks of sudden death, but there is uncertainty about making this information more generally available. (III)

Children want an explanation of the diagnosis. (III)

Families want provision of information, addressing concerns and concerns and fears, and providing emotional support as soon as possible after diagnosis. (III)

Details

Averis 1996[377]

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.

CSAG 2000[11]

The CSAG report stated that many older people would have liked counselling and more time with the doctor or nurse at the time of diagnosis.

Goldstein 1997[378]

In a UK survey of 94 adults with epilepsy attending a tertiary clinic, 73% of the 70 respondents at diagnosis were told what epilepsy was, but only 42% properly understood the explanation. 31.4% of respondents would have liked basic information on epilepsy (what it is, causes etc) - 40% would have liked extensive information (education, employment, leisure, benefits etc) and 17.1% would have liked both. 4.3% did not want to know more about epilepsy.

May 2002[379]

In an RCT to evaluate the use of an educational package to improve adults' knowledge and understanding of their epilepsy, there was no difference in the levels of improvement between those with a long and short duration of epilepsy (<=5 years vs >5 years). However, the authors suggested that it was reasonable to offer an educational program as soon as possible after diagnosis.

Buck 1996[380]

In a UK community based survey of 677 adults with epilepsy, the duration of epilepsy influenced the likelihood that individuals would discuss social implications; 79% of those with a reported duration of less than one year compared with only 59% of those with a duration of more than 10 years (difference in proportions 11, 95% CI 2 to 20). The authors suggested that this may be because individuals come to accept the social implications of epilepsy in time, or that doctors assume this to be the case. Another reason offered was that individuals believe that it is less appropriate to discuss social issues (as opposed to clinical issues) when there are time constraints in the consultation.

Ridsdale 2002[376]

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.

Ridsdale 1999[381]

In an interview study of adults with epilepsy (mean age 47 years, range 18 to 75 years) individuals felt that information about the diagnosis was extremely important. Specifically 3 individuals who had

been children when they were diagnosed reported that explanations were given to their parents, but not to them.

Austin 2002[382]

In a before and after study of an psychoeducational intervention study, comments from the 10 participant families of children with epilepsy indicated that the intervention would be most effectively administered early in the course of the disorder. The tailored intervention included provision of information, addressing concerns and concerns and fears, and providing emotional support.

Kennelly 2002[383]

In an interview study of 78 semi-structured interviews with the bereaved relatives of individuals with epilepsy who had died of SUDEP, several issues around the provision of information were identified. The relatives wanted 'information on epilepsy to be provided automatically to the individual either on or soon after diagnosis'. They also stressed the need for information to be given to carers as well as the individual with epilepsy to 'enable them to help them manage their condition, as well as to intervene effectively when they are unable to help themselves'.

Elwyn 2003[384]

Focus group interviews with 19 individuals with epilepsy identified both a lack of support at diagnosis and a lack of time and encouragement to express their concerns, which was particularly important at diagnosis.

Information needs and SUDEP

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

194. The risk of SUDEP can be minimised by:

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

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

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

Evidence statements

Bereaved relatives would like individuals with epilepsy to be presented with information on the risk of SUDEP during a face-to-face consultation by the responsible medical professional, either at or soon after diagnosis. (III)

Bereaved relatives need information from medical professionals to help them come to terms with the death of a person from SUDEP. (III)

Details

Kennelly 2002[383]

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.'*[383]

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

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

Details

As could be expected, there was considerable evidence on the information needs of individuals with epilepsy and others with regard to drug treatment, side effects, etc. However, no mention of preferred timing was given.

Other treatment

No evidence on the information needs of individuals on non-drug treatments could be found.

Remission

Mills 1997[385]

A UK questionnaire survey found that in 394 adults with epilepsy, people who had had an attack in the past 12 months were more likely to want discussion of topics (causes, side effects, laws etc),

significantly so for hospital attenders but not for GP attenders. However, the perceived adequacy of information was similar for both settings.

Refractory Epilepsy and Surgery

198. Information should be provided to children, young people and adults 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 informed consent is obtained. [2004]

Evidence statement

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

Swarztrauber 2003[386]

Focus group interviews were conducted with adults, including a sub-group of African Americans, and adolescents with refractory epilepsy, and their parents. The aim of the interviews was to determine how individuals felt about current treatments for refractory epilepsy and to describe their experiences.

Adults wanted more information on the surgical treatment of epilepsy. They also had perceptions of exaggerated risks of surgery, and many participants felt that surgery was a 'last ditch effort' and 'experimental'. Many adults felt that physicians portrayed surgery in a negative way.

Parents wanted their children to be able to take part in the decision about surgery when the child was old enough.

Special groups – see relevant section.

12.4 What is the risk of SUDEP in individuals with epilepsy

Evidence Statement

For those with severe epilepsy, a death rate of 1:200 per year can be estimated, whereas on a population basis the rate is between 1:500 and 1:1000 per year implying that for mild idiopathic epilepsy the rate is less than 1:1000. For those in remission the risk appears to be negligible. (III)

Details

A summary of the risk of death from SUDEP in key groups of people with epilepsy was requested by the GDG. This information could be used in recommendations on individual information and advice.

A systematic review of the literature relating to the incidence and prevalence of SUDEP and its possible risk factors was not done for reasons presented in Chapter 2.

The literature review on SUDEP from the SUDEP Report[18] is presented and a further review article was identified that summarized the available evidence on the mortality associated with epilepsy up to 1996.[387]

Secondary evidence

The National Sentinel Clinical Audit of Epilepsy-Related Death[18]

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.[17] 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.[388]

SUDEP is defined[389] as: 'sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in individuals with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomic cause for death.'

Case-control studies have been used to determine possible risk factors for SUDEP. Reported risk factors [390] 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.[391] 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.[391] Tomson,[392] 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.[393] 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.[390,391,394,395]

In line with other studies of risk it is important that the relative risk is not used alone as this does not indicate how common or uncommon the condition is in the population under study. It is important that an indication of the absolute risk of SUDEP is given in different population groups with epilepsy.

O'Donoghue 1997[387]

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.[387]

13 Women of childbearing age with epilepsy

13.1 Introduction

Most women with epilepsy who are receiving optimal treatment for their epilepsy, and who are well-informed, supported and fully counselled have uncomplicated pregnancies, normal deliveries, and healthy children.

However, there are a number of important health-related issues relating to the diagnosis of epilepsy and the use of AEDs in women of child-bearing age. First, both the disease and its treatment may alter the menstrual cycle and fertility. Second, there are problems with drug interactions, particularly with hormonal contraceptives. Some methods of hormonal contraception may not be as effective in women taking AEDS. The effectiveness will depend on which AED(s) are being taken. Effective contraception has an additional importance in women with epilepsy because of the risks associated with an unplanned pregnancy to the women and the developing fetus. Third, AEDs are associated with teratogenic effects. Fourth, AEDs and uncontrolled seizures can cause adverse effects during pregnancy. Conversely, pregnancy and the menstrual cycle can affect seizure control due to hormonally induced alteration of the seizure threshold.[396]

13.2 What information and counselling should be given and when?

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

200. Information about contraception, conception, pregnancy, or menopause should be given to women and girls in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with women and girls with epilepsy. These may include her family and/or carers. [2004]

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

Evidence statements

Women with epilepsy want, and need, information and counselling about issues relating to AED therapy and its effects, contraception, pregnancy, the risk of inheritance, and the menopause. (III)

Information is preferred before the time it is needed. (III)

Details

Secondary evidence

No systematic reviews of RCTs of information provision for women with epilepsy were identified.

One systematic review of other evidence was found. Couldridge and colleagues reviewed the primary evidence (including non-RCT studies) on the information and counselling needs of people with epilepsy, the preferred format, timing, and delivery of information and counselling, and the outcomes of information giving and counselling.[372]

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.

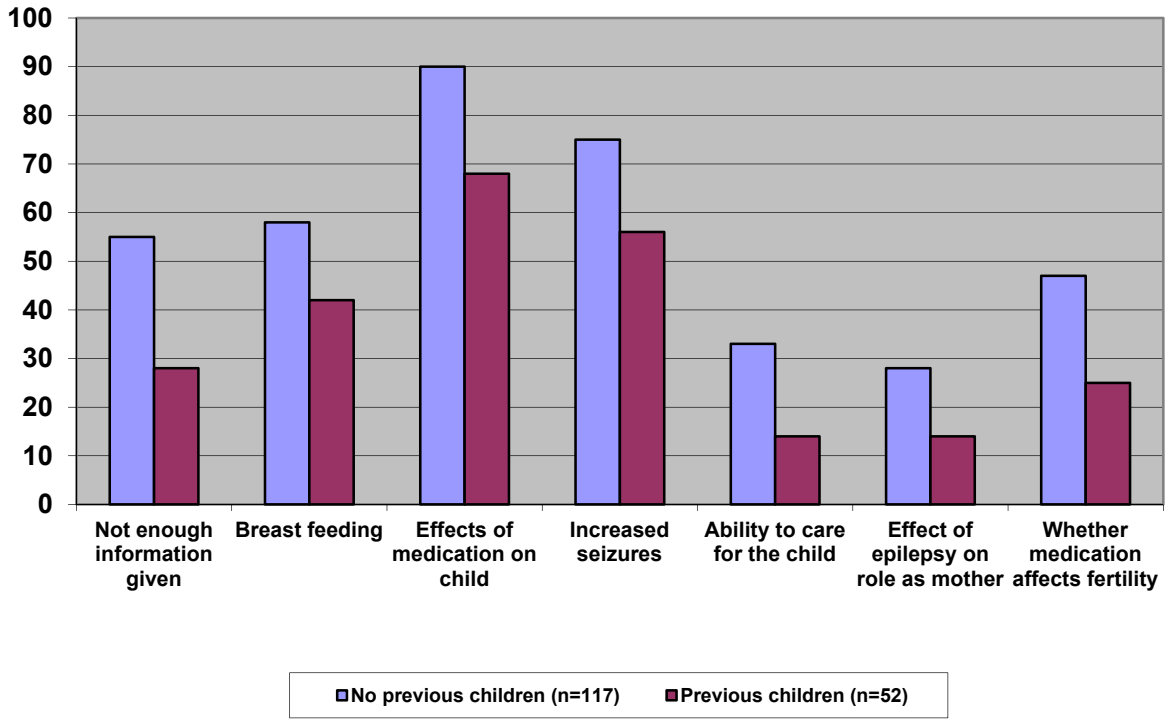
Since the publication of the systematic review described above[372], two large surveys of women with epilepsy were found.

Crawford 1999[397]

Crawford and Lee reported the results of a questionnaire survey of female members of the British Epilepsy Association. 1855 questionnaires (from a total of 6000) were included in the results (response rate 31%).

47% (n=89) of women taking oral contraception felt they had not been given enough information about the oral contraception pill and their AED(s). 43% (n=637) reported receiving no information about pregnancy, and 25% (n=459) had discussed pregnancy with no-one. Many women intending to have children in the subsequent two years felt they still had unanswered questions (see Figure 11-1).

Figure 2: Concerns about pregnancy[397] 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.[397]

Crawford 2003[398]

In 2001, the Ideal World survey aimed to assess the quality of current treatment information provision to women with epilepsy at different life stages, and to identify the information needs and wants with a view to ensuring that all women with epilepsy are counselled appropriately, in a timely manner, and are able to make informed choices about their treatment.

Approximately 12,000 female members of Epilepsy Action were surveyed, and the questionnaire was also posted on the Epilepsy Action website. 2,600 questionnaires and 90 web responses were completed, and 2000 responses randomly selected for analysis.

The most important issues for women aged 19 to 44 years who were considering having children were:

1. risk of epilepsy/medication affecting the unborn child (87%)
2. effect of pregnancy on seizure control (49%)
3. risk of a child developing epilepsy (42%)

For women aged 45 years or more, the most important issues were:

1. epilepsy medication and osteoporosis (63%)
2. epilepsy medication as you get older (57%)
3. changes in seizures during the menopause (44%).

Most women (84%) wanted to be better informed about treatment decisions, and 41% wanted to take a more proactive role in discussions around treatment. 43% wanted more information so they could ask for a review of their medication. 57% wanted the latest information on epilepsy treatment and the risk of birth defects on an ongoing basis, even if the data were incomplete.

The preferred timing of receiving information can be seen in 13.2.

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.[398]

13.3 What issues should be considered in women who may become pregnant or who are breast feeding?

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

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

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

205. All women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding for most women and girls taking AEDs is generally safe and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. [2004]

206. Prescribers should consult individual drug advice in the SPC and the BNF (available at http://bnf.org)[gg] when prescribing AEDs for women and girls who are breastfeeding. The decision regarding AED therapy and breastfeeding should be made between the woman or girl and the prescriber, and be based on the risks and benefits of breastfeeding against the potential risks of the drug affecting the child. [2004, amended 2012]

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

[gg] In this recommendation, the original referral to appendix 5 of the BNF has been removed and replaced with more up-to-date source reference material because this appendix no longer exists and has therefore become obsolete since the original guideline was published in 2004.

Issues are:

- increased risk of seizures
- teratogenic effects of AEDs
- effectiveness
- side sffects (see Section on on Pharmacological treatment)

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

13.4 Increased risk of seizures during pregnancy or whilst breastfeeding

Secondary evidence

No systematic reviews of seizure control during pregnancy were identified.

Primary evidence

Prospective cohort studies that assessed seizure frequency during pregnancy in women with epilepsy were included.

Five studies were identified that measured changes in seizure frequency during pregnancy (see 13.3). For each study different inclusion criteria were applied to participants, different time periods and different definitions of 'increased' or 'decreased' seizure rates were used. If no definition of seizure rate change was given, the study was excluded.

Table 29: Seizure frequency during pregnancy and puerperium

Study	Participants	Number of participants	Definition of seizure rate change(s)	Increased	Unchanged	Decreased
Bardy 1987[399]	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%34
Gjerde 1988[400]	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%
Schmidt 1983[401]	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[402]	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[403]	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	15%	61%	24%

[34] Percentages may not add to 100% due to rounding errors

Study	Participants	Number of participants	Definition of seizure rate change(s)	Increased	Unchanged	Decreased
			9 months prior to the pregnancy			

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[399,401,402] reported seizure frequency in the first 3 months after the birth.

Bardy found a statistically significant increase in complex focal seizures during the early puerperium ($p<0.001$).[399]

Increased seizures were seen in six pregnancies in the Schmidt study[401] and non-adherence and sleep deprivation were associated with five of these.

Tanganelli and Regesta[402] 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,[399] seizures occurred during labour in 10 cases, an incidence nine times greater than the average.

Bardy[404] also reported that a generalised tonic-clonic seizure occurred in labour in approximately 1-2% of women with epilepsy, and within 24 hours of delivery in another 1-2%.

There are two main sources of possible bias in all of the trials above:

1. because the history of seizure frequency before pregnancy relies on recall by the woman and her family (and in some studies, from medical records) there may be an underestimate of seizure frequency before pregnancy.
2. because none of the studies compare seizure rates in pregnant women with those in women who are not pregnant, some of the changes in rate may be due to random fluctuations in the epilepsy, rather than the effect of pregnancy.

13.5 Teratogenic effects of AEDs whilst pregnant

13.5.1 Introduction

It is recognised that an unborn child may be put at risk if exposed to toxins, of which alcohol and drugs, including prescribed medication are examples. Exposure to anti-epileptic drugs (AEDs) during pregnancy is associated with an increased risk of congenital malformations, and may have an adverse effect on fetal growth and psychomotor development. Although data on older AEDs and risk of congenital malformation has been evident, that on newer agents is only just being accumulated through pregnancy registries. Further, data on longer term effects on neurodevelopment of children exposed in utero can only be obtained through prospective study design. It is important that appropriate accurate information is made available to women so that informed choices can be made.

13.5.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included children of pregnant women with epilepsy who were exposed to one or more AEDs prior to delivery. Comparison groups included children of women with epilepsy who were not exposed to AEDs and children of women from the general population (without epilepsy). We looked for data specifically on the proportion of children born with major malformations, the proportion of children born with minor malformations, the incidence of miscarriage and developmental/cognitive outcomes. We found several systematic reviews for this review and therefore did not perform a review for individual studies. The systematic reviews included prospective controlled cohorts and case control studies.

When the systematic reviews provided information on the individuals included in the studies the results of each study were presented separately in this review. However, when the systematic reviews presented pooled data and a meta-analysis could be performed the results were presented in this way. This evidence review is divided in two sections based on the types of outcomes reviewed:

The first section presents evidence for minor/major malformations and miscarriage: We used a systematic review and meta-analysis (Meador, 2008) [405] of published pregnancy registries and cohorts to present the incidence of minor malformations, major malformations and miscarriage following in utero anti-epileptic drug exposure. This systematic review included studies with at least 100 total pregnancies or births.

The second section presents evidence for developmental/cognitive outcomes: We used a Cochrane review (Adab, 2004) [406] and a meta-analysis of cohort studies (Banach, 2010) [407] for information on the developmental/cognitive outcomes. Adab (2004) [406] included phenobarbital, phenytoin, carbamazepine, oxcarbazepine, sodium valporate, lamotrigine, topiramate, gabapentin, vigabatrin, tiagabine and zonisamide. These AEDs were either taken as monotherapy or polytherapy. The Banach (2010)[407] review included sodium valproate.

Table 30: Cognitive scales

Full name of the scale	Scales abbreviations	Brief description	Scoring
Bayley scales of development		An age standardised test of infant development between one month to 42 months. Measure development in 3 domains; cognitive, motor and behavioural.	Significant delay for scores with 2 SD below the mean, e.g. score<70.
Griffiths child development scale		Assess 5 areas of children development; locomotor, personal, social, hearing and speech, eye and hand co-ordination, performance. 2 scales for children 0-2 years and 2-8 years.	Each scale scored independently and summating all the subscales given the total DQ. Global delay is a DQ<70.
Wechsler Intelligence scale for children	WISC	A measure of general intellectual functioning for children aged 6-16 years.	12 subsets assessing 2 areas of intelligence: verbal IQ (VIQ) and performance (PIQ), summated provide a composite score (FSIQ).
Wechsler preschool and primary scale intelligence	WIPPSI	A measure of general intellectual functioning for children aged 6-16 years.	
Columbia Mental Maturity scale	CMMS	Assess general reasoning ability in children aged 3-9 years.	Raw score, age deviation score, percentile rank, stanine and maturity index.
Illinois test of psycholinguistic abilities	ITPA	A measure of used and acquisition of language for children aged 4-8 years.	10 subsets and 2 supplementary subsets. Raw scores used to derive a composite score,

Full name of the scale	Scales abbreviations	Brief description	Scoring
			psycholinguistic age scores and psycholinguistic quotients for subtests and composite.
Frostig test of visual perception	FTVP	Assess visual perception skills in children aged 4-8 years.	5 subsets. Raw scores obtained for each subset and converted to age equivalents or perceptual ages (Pas) and Scale Scores (SS); total score expressed in Perceptual Quotient.
Lincoln Oseretzky test of Motor Performance	LOS	A measure of motor performance for children 6-14 years.	36 subscales. Scores presented as percentile ranks for each age level.
McCarthy Scales	McC	A measurement device to assess the abilities of preschool children 2.5-8.5 years.	Six scale scores: verbal, perceptual-performance, quantitative, general cognitive, memory, motor.
Leiter international performance scale	LIPS	Non verbal test of intelligence. Assess intellectual ability, memory and attention for those whom traditional test could not be used between 2-20 years.	2 main batteries; visualisation and reasoning (VR) and attention and memory (AM). Each battery provides a measure of IQ SCORES.
Neuropsychological test battery adapted from Luria	NEPS	A standardized test battery used in the screening and evaluation of neuropsychologically impaired individuals 13 years old and older	It consists of 269 items in 11 clinical scales. Scores for three summary scales can also be calculated: pathognomonic, right hemisphere, and left hemisphere.
School career		Being in inappropriate class for age and learning disorders	Frequency (proportion)
Dutch test		3 subtests; reading, spelling, arithmetic.	Proportion of children with score< 10th centile

13.5.2.1 Incidence of malformations

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Congenital malformations- statistically significant results

Significantly more children (including those of pregnancies that did not come to term) of women taking the following AEDs had congenital malformations compared to general population:

- sodium valproate
- phenobarbital and one other AED
- phenytoin and one other AED
- sodium valproate and one other AED
- phenobarbital and two other AEDs
- phenytoin and two other AEDs
- sodium valproate and two other AEDs

Significantly more children of women taking the following AEDs were born with congenital malformations compared to general population:

- carbamazepine
- sodium valproate

Cost-effectiveness

No economic evidence comparing exposure to any AED to non-exposure in the general population was identified.

13.5.2.2 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to monotherapy compared to general population

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Congenital malformations/other pregnancy outcomes- statistically significant results

The incidence of stillbirth was significantly higher in children exposed in utero to monotherapy with antiepileptic medication compared to children in general population, however there is uncertainty over the magnitude of its effect. (VERY LOW QUALITY)^

The incidence of spontaneous abortions was significantly higher in children in general population compared to children exposed in utero to monotherapy. (VERY LOW QUALITY) ^

The incidence of elective abortions was significantly higher in children in general population compared to children exposed in utero to monotherapy. (VERY LOW QUALITY) ^

The incidence of births with congenital malformation was significantly higher in children exposed in utero to monotherapy compared to children in general population. (VERY LOW QUALITY) ^

The incidence of perinatal deaths was significantly higher in children exposed in utero to monotherapy compared to children in general population. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any monotherapy to non-exposure in the general population was identified.

13.5.2.3 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to polytherapy compared to general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Congenital malformations/other pregnancy outcomes- statistically significant results

The incidence of spontaneous abortions was significantly higher in children in general population compared to children exposed in utero to polytherapy. (VERY LOW QUALITY) ^

The incidence of elective abortions was significantly higher in children in general population compared to children exposed in utero to polytherapy. (VERY LOW QUALITY) ^

The incidence of elective abortions due to malformations was significantly higher in children exposed in utero to polytherapy compared to children in general population, however there is uncertainty over the magnitude of its effect. (VERY LOW QUALITY) ^

The incidence of births with congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY) ^

The incidence of congenital malformations (total events) was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY)

The incidence of perinatal deaths was significantly higher in children exposed in utero to polytherapy compared to children in general population. (VERY LOW QUALITY) ^

Cost-effectiveness

No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.2.4 Incidence of congenital malformations/other pregnancy outcomes in children exposed in utero to monotherapy compared to polytherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Congenital malformations/other pregnancy outcomes- statistically significant results

The incidence of births with congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in monotherapy. (VERY LOW QUALITY)

The incidence of congenital malformation was significantly higher in children exposed in utero to polytherapy compared to children in monotherapy. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any polytherapy to exposure to any monotherapy was identified.

13.5.3 Comparison between specific monotherapies on developmental /cognitive outcomes

13.5.3.1 Phenytoin versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/Cognitive outcomes –statistically non significant results

No significant difference between phenytoin monotherapy and carbamazepine monotherapy for the following developmental/cognitive scales:

- Bayley scale (mental, motor, language, cognitive) (VERY LOW QUALITY)
- McCarthy scale of children's abilities (GCI T, verbal, perceptual, quantitative, memory, motor over 30 months (VERY LOW QUALITY)
- Reynell standard scores (comprehension, expressive) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenytoin monotherapy to carbamazepine monotherapy was identified.

13.5.3.2 Phenytoin versus phenobarbital

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically non significant results

No significant difference between phenytoin monotherapy and phenobarbital monotherapy for the following developmental/cognitive scales:

- Gesell developmental schedules (VERY LOW QUALITY)
- mental development (8 months) (VERY LOW QUALITY)
- motor development (8 months) (VERY LOW QUALITY)
- IQ (4 years) (VERY LOW QUALITY)
- WISC/WPPSI (4-9 years) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing phenytoin monotherapy to phenobarbital monotherapy was identified.

13.5.3.3 Phenobarbital versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically non significant results

No significant difference between phenobarbital monotherapy and carbamazepine monotherapy for the Dutch test (non optimal school career, poor reading, poor arthemetic, poor spelling) (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing phenobarbital monotherapy to carbamazepine monotherapy was identified.

13.5.3.4 Sodium valproate versus carbamazepine

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to sodium valproate monotherapy scored significantly lower compared to children exposed to carbamazepine monotherapy in utero for:

- WPPSI/WISC revised verbal IQ scale, however there is uncertainty over the magnitude of this effect. (VERY LOW QUALITY)
- Bayley scales – mental and differential ability scale, however there is uncertainty over the magnitude of this effect. (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the proportion of children with mild to severe developmental delay (4mths – 10 years)

No significant difference between sodium valproate monotherapy and carbamazepine monotherapy for the following developmental/cognitive scales:

- WPPSI/WISC revised non verbal IQ scale (VERY LOW QUALITY)
- WPPSI/WISC revised full scale (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to carbamazepine monotherapy was identified.

13.5.3.5 Sodium valproate versus phenytoin

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically non significant results

No significant difference on the Bayley scale in children exposed to sodium valproate and phenytoin. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to phenytoin monotherapy was identified.

13.5.3.6 Sodium valproate versus lamotrigine

Clinical Evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to sodium valproate scored significantly lower on the Bayley scale compared to children exposed to lamotrigine. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to lamotrigine monotherapy was identified.

13.5.4 Any monotherapy exposure versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to monotherapy scored significantly lower compared to non exposed children in general population for:

- WPPSI (performance and total scale) (10-20 years) (VERY LOW QUALITY)
- LOS scale (4-6 years) (VERY LOW QUALITY)
- WISC performance IQ (10-19 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to monotherapy and non exposed children in general population for the proportion of children with borderline intelligence and children with learning disabilities (VERY LOW QUALITY)

No significant difference between children exposed to monotherapy and non exposed children in general population for the following developmental/cognitive scales:

- Bayley Scales (mental, motor) (15 months) (VERY LOW QUALITY)
- WPPSI (verbal, performance) (4-6 years) (VERY LOW QUALITY)
- CMMS scale (4-6 years) (VERY LOW QUALITY)
- WPPSI (verbal) (10-20 years) (VERY LOW QUALITY)
- ITPA scale (4-6 years) (VERY LOW QUALITY)
- FTVP scale (4-6 years) (VERY LOW QUALITY)
- McCarthy T scores (4-6 years) (VERY LOW QUALITY)
- WISC scale (verbal, total IQ) (10-19 years) (VERY LOW QUALITY)

- WPPSI (5.5 years) (VERY LOW QUALITY)
- LIPS scale (5.5 years) (VERY LOW QUALITY)
- WPPSI-R (verbal, non verbal, full scale) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any monotherapy to non-exposure in the general population was identified.

13.5.4.1 Carbamazepine exposure versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to carbamazepine scored significantly lower compared to non exposed children in general population for:

- McCarthy GCI, verbal, perceptual, quantitative, memory and motor scores (early years) (VERY LOW QUALITY)
- Bayley mental development index (early years) (VERY LOW QUALITY)^
- McCarthy Global development index (early to school years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to carbamazepine and non exposed children in general population for the following developmental/cognitive scales:

- Reynell Scales (comprehension, expressive) (early years) (VERY LOW QUALITY)
- Bayle Scales (mental, performance, cognitive, language, motor) (early years) (VERY LOW QUALITY)
- Griffiths child development scale (early years, early to school years) (VERY LOW QUALITY)
- McCarthy (early to school years) (VERY LOW QUALITY)
- Dutch test for poor outcomes (reading, spelling, arithmetic, school career) (early to school years) (VERY LOW QUALITY)
- WPPSI-R/WISC-R (verbal, non verbal IQ, full scale) (early to school years) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to carbamazepine to non-exposure in the general population was identified.

13.5.4.2 Phenytoin exposure versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to phenytoin scored significantly lower compared to non exposed children in general population for:

- Bayley scale-language (early to school years) (LOW QUALITY)
- McCarthy scale (GCI, verbal, perceptual, quantitative) ((early to school years) (LOW UALITY)^
- Reynell scale (comprehension, expressive) (early to school years) (LOW QUALITY)
- IQ (4 years) (LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to phenytoin and non exposed children in general population for the following developmental/cognitive scales:

- Griffiths child development index (VERY LOW QUALITY)
- Mental scale (specific tests not detailed) (8 months) (VERY LOW QUALITY)
- Motor scale (specific tests not detailed) (8 months) (VERY LOW QUALITY)
- Gesell development quotient (VERY LOW QUALITY)
- Bayley scales (MDI, PDI, cognitive, language, motor) (VERY LOW QUALITY)
- McCarthy scales (memory, motor) (VERY LOW QUALITY)
- WISC/WIPPSI (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to phenytoin to non-exposure in the general population was identified.

13.5.4.3 Phenobarbital exposure versus those no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Significantly more children exposed to phenobarbital compared to non exposed children in general population had low scores (<10th centile) in:

- Dutch test for spelling (LOW QUALITY)
- Dutch test for arithmetic (LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to phenobarbital and non exposed children in general population for the following developmental/cognitive scales:

- Mental development scale (specific tests not detailed) (VERY LOW QUALITY)
- Motor development scale (specific tests not detailed) (VERY LOW QUALITY)
- Gesell development quotient (VERY LOW QUALITY)
- IQ test (not specified) (VERY LOW QUALITY)
- Dutch test for reading (VERY LOW QUALITY)
- School career (VERY LOW QUALITY)
- WISC/WIPPSI (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to phenobarbital to non-exposure in the general population was identified.

13.5.4.4 Sodium valproate exposure versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically significant results

Children exposed to sodium valproate scored significantly lower than non exposed children in the general population in the WPPSI-R/WISC-R verbal IQ scale. (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non-significant results

No significant difference was found on either scale of IQ (performance and full scale) between children exposed to sodium valproate in utero and general population (non exposed children of non epileptic mothers) (VERY LOW QUALITY).

No significant difference was found on non verbal and full scale of WPPSI-R/WISC-R between children exposed to sodium valproate in utero and general population (non exposed children of non epileptic mothers) (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing exposure to sodium valproate to non-exposure in the general population was identified.

13.5.4.5 Comparison of any AED versus no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to any AED compared to non exposed children in general population had significantly low scores in:

- Bayley scale (motor, home inventory) (15 months) (VERY LOW QUALITY)
- Gesell development scale (18-36 months) (VERY LOW QUALITY)
- Enjohiji's test (fundamental habits, human relationships, speech, language in infants < 24 months) (fundamental habits, body movement, hand movement , human relationships, speech, language in infants 24-53 months) (VERY LOW QUALITY)
- WPPSI scale (5.5 years) (VERY LOW QUALITY)
- LIPS scale (5.5 years) (VERY LOW QUALITY)
- proportion of children with specific cognitive dysfunction (VERY LOW QUALITY)
- WPPSI scale (verbal, performance) (4-6 years) (VERY LOW QUALITY)
- CMMS scale (VERY LOW QUALITY)
- FTVP scale (VERY LOW QUALITY)
- LOS scale (VERY LOW QUALITY)
- WPPSI/WISC scale (proportion of children with IQ<90) (4-9 years) (VERY LOW QUALITY)
- WPPSI/WISC scale (proportion of children with language disability), however there is uncertainty over the magnitude of its effect (4-9 years) (VERY LOW QUALITY)
- WPPSI/WISC scale (full scale) (4-8 years) (VERY LOW QUALITY)
- WISC scale (verbal, performance) (4-8 years) (VERY LOW QUALITY)
- VMI scale (4-8 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to any AED and non exposed children in general population for the following developmental/cognitive scales:

- Griffiths development scale (VERY LOW QUALITY)
- Enjohiji's test (body, hand movement in infants<24 months) (VERY LOW QUALITY)
- Proportion of children with mental deficiency, borderline intelligence (5.5 years) (VERY LOW QUALITY)
- ITPA scale (VERY LOW QUALITY)
- McCarthy scale (VERY LOW QUALITY)
- WPPSI/WISC scale (proportion of children with learning disabilities) (4-9 years) (VERY LOW QUALITY)
- WPPSI/WISC scale (proportion of children with special education needs) (4-9 years) (VERY LOW QUALITY)
- ITPA (auditory association, grammatic closure) (4-8 years) (VERY LOW QUALITY)
- Griffiths scale (locomotor function, personal and social behaviour, hearing and speech, eye and hand coordination, performance, practical reasoning) (VERY LOW QUALITY)
- Dutch test (reading, spelling, arithmetic) (7-13 years) (VERY LOW QUALITY)
- School career (7-13 years) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any AED to non-exposure in the general population was identified.

13.5.4.6 Any polytherapy exposure versus those no exposure in general population

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to polytherapy compared to non exposed children in general population had significantly low scores in:

- Bayley Motor scale (15 months) (VERY LOW QUALITY)
- CMMS scale (4-6 years) (VERY LOW QUALITY)
- ITPA scale (4-6 years) (VERY LOW QUALITY)
- WPPSI verbal scale (4-6 years) (VERY LOW QUALITY)
- WPPSI performance scale (4-6 years) (VERY LOW QUALITY)

- McCarthy scale (4-6 years) (VERY LOW QUALITY)
- WPPSI scale (verbal, performance, total scale) (10-20 years) (VERY LOW QUALITY)
- WPPSI-R/WISC-R verbal IQ scale (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:

- Bayley Mental scale (15 months) (VERY LOW QUALITY)
- proportion of children with mild-severe developmental delay (early to school years) (VERY LOW QUALITY)
- FTVP scale (4-6 years) (VERY LOW QUALITY)
- LOS scale (VERY LOW QUALITY)
- WISC scale (verbal IQ, performance IQ, total IQ) (10-19 years) (VERY LOW QUALITY)
- proportion of children with borderline intelligence (VERY LOW QUALITY)
- proportion of children with learning disability (VERY LOW QUALITY)
- WPPSI-R/WISC-R scale (non verbal IQ, total scale) (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.4.7 Any AED exposure in utero versus no exposure in children of mothers with epilepsy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes- statistically significant results

Children exposed to polytherapy compared to non exposed children in general population had significantly low scores in:

- WPPSI Performance scale (4-6 years) (VERY LOW QUALITY)

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:

- Bayley scale (mental, motor, home inventory) (15 months) (VERY LOW QUALITY)
- WPPSI scale (5.5 years) (VERY LOW QUALITY)

- LIPS scale (5.5 years) (VERY LOW QUALITY)
- Dutch test (reading, spelling, arithmetic) (VERY LOW QUALITY)
- School career (7-13 years) (VERY LOW QUALITY)
- WPPSI Verbal scale (4-6 years) (VERY LOW QUALITY)
- ITPA scale (4-6 years) (VERY LOW QUALITY)
- FTVP scale (4-6 years) (VERY LOW QUALITY)
- LOS scale (4-6 years) (VERY LOW QUALITY)
- McCarthy scale (4-6 years) (VERY LOW QUALITY)
- WPPSI scale (verbal, performance, total IQ) (10-20 years) (VERY LOW QUALITY)
- proportion of children with borderline intelligence (VERY LOW QUALITY)
- proportion of children with learning disability (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.4.8 Any monotherapy exposure versus no exposure in children of mothers with epilepsy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically non significant results

No significant difference between children exposed to polytherapy and non exposed children in general population for the following developmental/cognitive scales:

- Dutch test (reading, spelling, arithmetic) (7-13 years) (VERY LOW QUALITY)
- school career (7-13 years) (VERY LOW QUALITY)
- WISC scale (verbal, performance, total IQ) (10-19 years) (VERY LOW QUALITY)
- WPPSI scale (verbal, performance, total IQ) (VERY LOW QUALITY)
- proportion of children with borderline intelligence (VERY LOW QUALITY)
- proportion of children with learning disability (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing exposure to any polytherapy to non-exposure in the general population was identified.

13.5.4.9 Carbamazepine exposure versus no exposure to children of women with epilepsy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically non significant results

No significant difference was found on any scale of WPPSI-R/WISC-R between children exposed to carbamazepine in utero and children of women with epilepsy not exposed to carbamazepine in utero. (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing exposure to carbamazepine to non-exposure in women with epilepsy was identified.

13.5.4.10 Sodium valproate exposure versus no exposure to children of women with epilepsy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Developmental/cognitive outcomes – statistically significant results

Children exposed to sodium valproate scored significantly lower than non exposed children of women with epilepsy in:

- WPPSI-R/WISC-R verbal IQ (VERY LOW QUALITY).

Developmental/cognitive outcomes – statistically non significant results

No significant difference was found on WPPSI-R/WISC-R (non verbal, full scale) between children exposed to sodium valproate in utero and non exposed children of epileptic mothers (VERY LOW QUALITY).

No significant difference was found on either scale of IQ (verbal, performance and full scale) between children exposed to sodium valproate in utero and non exposed children of epileptic mothers (VERY LOW QUALITY).

Cost-effectiveness

No economic evidence comparing exposure to sodium valproate to non-exposure in women with epilepsy was identified.

13.5.5 New recommendations and link to evidence

Recommendation	**207. Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. [new 2012]**
Relative values of different outcomes	The GDG placed greater importance on the incidence of major malformations, miscarriages and neurodevelopmental outcomes for the child of a mother with epilepsy.
Trade off between clinical benefits and harms	The risk of harm to mother and unborn child from seizures needs to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. Drugs and doses that may be cost-effective in the general epilepsy population, such as sodium valproate, may not be as cost-effective in this group due to its potential teratogenic effect.
Quality of evidence	Evidence comes from three systematic reviews; one review focused on incidence of malformation and the other two on child neurodevelopmental outcomes. No individual RCTs were reviewed. This recommendation was also based on GDG consensus opinion.
Other considerations	This recommendation was updated and amended from the first edition of this guideline (2004).

Recommendation	***208.*** **Be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of present and future childbearing potential. [2012]**
Relative values of different outcomes	Seizure freedom and adverse events in the mother and malformations and neurodevelopmental delay in the child were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Risks of seizure exacerbation or relapse with reduction in dose of AED need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. The GDG felt that if health care professionals are aware of the most up to date data on the teratogenic risks of different AEDs, then well informed prescribing decisions can be made.
Quality of evidence	This recommendation was based on GDG consensus opinion.
Other considerations	This recommendation is unchanged from the 2004 edition of this guideline. The GDG considered this recommendation to be still valid in light of the reviewed evidence for the 2012 update.

Recommendation	**209. Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalised tonic–clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of each AED, avoiding polytherapy if possible. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse events in the mother and malformations and neurodevelopmental delay in the child were considered to be the most important outcomes.
Trade off between clinical benefits and harms	Risks of seizure exacerbation/relapse with reduction in dose of AED need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	No economic evidence was available to inform the GDG on cost-effectiveness of AEDs used to treat pregnant women with epilepsy. No economic evaluation has ever incorporated teratogenicity into its clinical outcomes. The GDG considered that both reduced seizure control and potential harms (malformations and neurodevelopmental delay) have cost and quality of life implications for mother and unborn child. Drugs and doses that may be cost-effective in the general epilepsy population, such as sodium valproate, may not be as cost-effective in this group due to its potential teratogenic effect.
Quality of evidence	This recommendation was based on GDG consensus opinion.
Other considerations	None.

Recommendation	**210. Discuss with women and girls who are taking lamotrigine that the simultaneous use of any oestrogen-based contraceptive can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When a woman or girl starts or stops taking these contraceptives, the dose of lamotrigine may need to be adjusted. [new 2012]**
Relative values of different outcomes	Seizure freedom, adverse effect and effective contraceptive were considered the most important outcomes.
Trade off between clinical benefits and harms	Interaction between lamotrigine and any oestrogen-based contraceptive may reduce lamotrigine's anticonvulsant effect because of hepatic metabolism.
Economic considerations	There was no economic evidence available and this type of scenario was not incorporated into the original economic models undertaken for the guideline. However, the GDG considered that the likely extra resource use and costs associated with adjusting dosage (extra medical appointments and/or increased or decreased daily dose) was likely to be cost-effective if it helps to maintain seizure control.
Quality of evidence	This recommendation was based on GDG consensus opinion.

Other considerations	None.

Recommendation	**211. Do not routinely monitor AED levels during pregnancy. If seizures increase or are likely to increase, monitoring AED levels (particularly levels of lamotrigine and phenytoin, which may be particularly affected in pregnancy) may be useful when making dose adjustments. [new 2012]**
Relative values of different outcomes	Seizure freedom and adverse effect were considered the most important outcomes.
Trade off between clinical benefits and harms	Risks of seizure exacerbation/relapse with alteration in pharmacokinetics of AED in pregnancy need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	There was no economic evidence available on routine monitoring of AED levels and this was not incorporated into the original economic models undertaken for the guideline. The GDG considered that routine monitoring of AED levels in pregnancy is not necessary. However, it should be borne in mind that the levels of some AEDs, and specifically lamotrigine and phenytoin, may be affected by pregnancy and monitoring of these levels may reduce the risk of seizures that may cause harm to the mother and the unborn child.
Quality of evidence	This recommendation was updated from the first edition of this guideline (2004).
Other considerations	None.

Recommendation	**212. 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 (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)** • **specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy (see recommendation 211) [2012]**
Relative values of different outcomes	Seizure freedom and adverse effect were considered the most important outcomes.
Trade off between clinical benefits and harms	Risks of seizure exacerbation/relapse with alteration in the pharmacokinetics of AEDs in pregnancy need to be balanced against the risk of harm from antiepileptic medication taken by the mother in pregnancy.
Economic considerations	There was no economic evidence available on routine monitoring of AED levels and this was not incorporated into the original economic models undertaken for the guideline. The GDG considered that there are some specific indications for monitoring of AED blood levels, such as detection of non-adherence to the prescribed medication, suspended AED toxicity, adjustment of phenytoin dose and/or management of pharmacokinetic interactions. Routine monitoring of AED levels in pregnancy is not necessary, however, it should be borne in mind that the levels of some AEDs particularly lamotrigine and phenytoin may be affected by pregnancy and monitoring of these levels may reduce the risk of seizures that may cause harm to the mother and the unborn child.
Quality of evidence	This recommendation was updated from the first edition of this guideline (2004).
Other considerations	None.

Recommendation	**213. Refer to the SPC and BNF (available at http://www.bnf.org) for individual drug advice on the interactions between AEDs and hormonal replacement and contraception. [new 2012]**
Relative values of different outcomes	Seizure freedom, adverse effect and effective contraceptive were considered the most important outcomes.
Trade off between clinical benefits and harms	The risks of unplanned pregnancy caused by drug interaction between AEDs and hormonal contraceptives must be considered, but the risks of seizures require that, when possible, the most effective antiepileptic medication be prescribed.
Economic considerations	There was no economic evidence available and concomitant use of AEDs and hormonal contraceptives was not incorporated into the original economic models undertaken for the guideline. However, the GDG considered that interactions between AEDs and hormonal contraceptives should be borne in mind to reduce the risk of unplanned pregnancies or reduced seizure control.
Quality of evidence	This recommendation was based on GDG consensus opinion.
Other considerations	None.

13.5.6 New research recommendations (for full list see section 2.11)

13.5.6.1 AEDs and pregnancy

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

Why this is important

Pregnancy registers are increasing the data that are available on established AEDs; however, these registers may give malformation rates but do not provide controlled long-term data on neurodevelopmental outcome.

The research should include:

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

13.6 Do AEDs interact with contraceptives?

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

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

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

217. If a woman or girl taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, guidance about dosage should be sought from the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012]

218. The progestogen[♣]-only pill is not recommended as reliable contraception in women and girls taking enzyme-inducing AEDs. [2004, amended 2012]

219. The progestogen[gg] implant is not recommended in women and girls taking enzyme-inducing AEDs. [2004, amended 2012]

220. The use of additional barrier methods should be discussed with women and girls taking enzyme-inducing AEDs and oral contraception or having depot injections of progestogen[ii]. [2004, amended 2012]

221. If emergency contraception is required for women and girls taking enzyme-inducing AEDs, the type and dose of emergency contraception should be in line with the SPC and current edition of the BNF (available at http://bnf.org). [2004, amended 2012]

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.[43,408]

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

[♣] In this recommendation, 'progesterone' has been replaced with 'progestogen' to reflect a change in terminology since the original guideline was published in 2004.

[ii] In this recommendation, 'progesterone' has been replaced with 'progestogen' to reflect a change in terminology since the original guideline was published in 2004.

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 2002[409]

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 progestogen-only pill is likely to be unreliable in women taking enzyme-inducing AEDs.
- (Based on the BNF)
- The frequency of injection for depot progestogen should be increased to every 10 weeks (compared with the usual 12 weeks) in women taking enzyme-inducing AEDs.
- (Based on expert opinion only)
- Progestogen 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.[396]

Oral contraception ('The pill')

Coulam 1979[410]

In 1979, Coulam and Annegers presented the results of a record review of 82 women with epilepsy who were also taking oral contraception.[410] 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.[410]

Back 1988[411]

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 phenobarbital, 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.[411]

No evidence was found on the most effective dose of oral contraception, or the most effective regimen. A recent guideline[396] on the management of women with epilepsy recommended, on the basis of evidence and consensus, that

- For women on enzyme-inducing AEDs (phenytoin, phenobarbital, 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).[396]

Hormone-releasing intrauterine devices

Bounds 2002[412]

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, phenobarbital, primidone, and topiramate.

During the 1,075 months of exposure to the risk of pregnancy, two accidental pregnancies were reported, both to women taking AEDs (primidone and phenytoin, and phenytoin only). Only one of these was assessed as being a true failure event; the other failure may have been due to a non-protected period after removal of the IUD. The failure rate was calculated to be 1.1 per 100 woman-years (95% CI 0.03 to 6.25) based on the true failure only, and 2.2 per 100 woman-years (95% CI 0.27 to 8.07) based on both failures.

The authors stressed that this was a pilot study only, but that the failure rate of 2.2 per 100 woman-years compared well with failure rates for women on oral contraception and AEDS (approximately 7 per 100 woman-years[396], and was better than rates for barrier methods (15 to 20 per 100 woman-years).[396,412]

Progesterone implants

Haukamaa 1986[413]

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 the12 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[414]

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.[414]

The use of an increased dose was also proposed in another review of emergency contraception,[415] 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'.[396]

13.7 Does epilepsy increase the risk of complications in pregnancy?

222. Women and girls 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 and girls without epilepsy. [2004]

223. Care of pregnant women and girls should be shared between the obstetrician and the specialist. [2004]

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

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

Evidence statements

Most women with epilepsy have healthy pregnancies however they may have an increased risk of complications. (IIa)

Prenatal screening can identify some abnormalities. (Ia NICE)

13.7.1 Are women with epilepsy at increased risk of complications during the pregnancy and labour?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Fairgrieve 2000[416]

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.[416]

Tanganelli 1992[402]

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%).[402]

Olafsson 1998[417]

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.[417]

13.7.2 When should screening for structural fetal anomalies be performed in pregnant women with epilepsy?

A recent NICE guideline reviewed the evidence on the detection of structural fetal abnormalities in healthy pregnant women.[418] 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'.[418]

13.8 When should folic acid be started?

226. All women and girls on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy. [2004]

Evidence statement

There is limited evidence to show that folic acid supplementation reduces the risk of NTD and other congenital malformations in women taking AEDs. (IV)

Details

This was not subject to a full evidence review for reasons given in Chapter 2.

Folates and folic acid have a major role to play in the prevention of neural tube defects.[419]

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.[419]

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

A narrative review[420] 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.'[420]

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

227. Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and SUDEP should be discussed with all women and girls who plan to stop AED therapy (see section 10.2.6). [2004]

228. Women and girls 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. [2004]

229. Women and girls should be reassured that there is no evidence that focal[jj], absence and myoclonic seizures affect the pregnancy or developing fetus adversely unless they fall and sustain an injury. [2004, amended 2012]

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

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

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

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

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

Evidence statements

There is no evidence that simple focal, complex focal, absence and myoclonic seizures adversely affect the pregnancy or developing fetus. (IV)

Generalised tonic-clonic seizures are likely to result in more profound hypoxia than in the non-gravid state due to increased maternal oxygen requirements. This may have adverse affects for the fetus. (IV)

Indirect deaths from medical conditions exacerbated by pregnancy were greater than those deaths from conditions directly arising from pregnancy. Some of these deaths were attributed to epilepsy. (III)

Babies of mothers with active epilepsy, particularly if the mother has juvenile myoclonic epilepsy, are at risk of injury. The risk of injury is related to seizure type and severity. In particular, the pattern of seizures is crucial. (III)

Details

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

Effects of maternal seizures on the fetus

An expert workshop convened by the Epilepsy Research Foundation[421] considered both published evidence and expert opinion and concluded that:

- Focal seizures and non-convulsive generalised seizures are unlikely to expose the fetus to immediate risks in utero.

[jj] In this recommendation, 'partial seizures' has been replaced with 'focal seizures' to reflect a change in terminology since the original guideline was published in 2004.

[kk] Appendix D provides a checklist for the information needs of women and girls with epilepsy, and practical information for mothers with epilepsy.

- 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.[421]

Effect of maternal seizures on the woman

The Confidential Enquires into Maternal Deaths in the United Kingdom[422] 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.[422]

Effect of maternal seizures during labour

The expert workshop[421] 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 1999[423]

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.[423]

13.10 What is the role of drug monitoring in pregnant women with epilepsy?

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.[148]

13.11 Should oral or parenteral vitamin K be used?

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

Evidence statement

There is limited evidence to show that the risk of haemorrhagic disease of the newborn is not increased in women taking enzyme-inducing AEDs provided that infants receive the standard treatment of 1mg vitamin K parenterally (intra-muscular or intra-venous) at birth. (III)

Details

This was not subject to a full evidence review for reasons given in Chapter 2.

No systematic reviews or RCTs comparing oral and parenteral vitamin K were identified. Only one prospective study was identified.

Kaaja 2002[424]

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.[424]

13.12 What is the risk of of inheriting epilepsy?

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

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

Evidence statements

For idiopathic generalized epilepsy, the risk of a child developing the condition is 5–20% if there is one affected first degree relative (including the mother), and over 25% if two first degree relatives are affected. Thus the risk of a individual with idiopathic generalized epilepsy having an affected child is about 9–12%, and the risk is 3% in children of those with cryptogenic (focal) 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 (focal) seizures.[396]

13.13 What is the role of joint epilepsy and obstetric clinics in the care of women with epilepsy who are pregnant?

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

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

Evidence statement

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

Details

No systematic reviews or RCTs were identified.

14 Children, young people and adults with learning disabilities and epilepsy

14.1 Introduction

The prevalence of learning disabilities in the population is approximately 18 per 1000. Thus, a GP with a list size of 2000 has approximately 36 individuals with learning disabilities, of whom about six will have severe learning disabilities. Epilepsy and learning disabilities commonly co-exist and most often develop in childhood. It is estimated that epilepsy has a prevalence of 15% in people with mild learning disabilities and 30% in those with severe learning disabilities.

People with mild learning disabilities (IQ 50 to 70) and no other concomitant conditions are at lowest risk (5-7%) of developing epilepsy. Up to 75% of those with additional disabilities such as cerebral palsy or postnatal brain injury have epilepsy. Severe learning disability (IQ 20 to 50) is more likely in individuals with early seizure onset. People with Down's syndrome and other chromosomal conditions commonly have epilepsy: approximately 8-10% of such people have a history of seizures. Many children with epilepsy do not have associated learning disabilities, but some childhood onset epilepsies, such as Lennox-Gastaut syndrome, are associated with learning disabilities.[425]

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.[426]

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 field[427] 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.[427]

14.2 Who should manage and treat epilepsy in children, young people and adults with learning disabilities?

Evidence statements

No studies were identified that compared outcomes for people with epilepsy and learning disabilities managed by different groups of clinicians. In particular, there was no comparison of 'specialist' versus 'non-specialist' care.

There was one study that suggested that specialists may be better at managing learning disabilities with epilepsy. (III)

14.2.1 Do people with learning disabilities and epilepsy who receive care from a specialist in learning disabilities and epilepsy compared with care from a non-specialist have differences in processes and outcomes of care?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Collacott 1989[428]

A cohort of 215 people (mean age 38 years±14 years) with learning disabilities and epilepsy was followed-up for four years. The participants were all residents of a mental handicap unit in the UK. The anticonvulsant regimes were reviewed by a specialist in mental handicap and a specialist in clinical pharmacology. Of the 172 who remained in the study, 41% were seizure free compared with 37% on the initial review ($p<0.005$). Overall, seizure frequency was reduced in 48%, increased in 33% and unchanged in 19%. At the final review, the mean number of AEDs per individual was reduced from 1.41 to 1.05 ($p<0.005$).[428]

Although this study suggests that specialists are better at managing PLD and epilepsy, there was no description of who managed the individuals prior to the assessment.

DeToledo 2002[429]

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%).[429]

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

14.3 Is making a diagnosis more difficult in people with learning disabilities?

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

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

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

Evidence statements

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

14.3.1 Are the rates of misdiagnosis higher for people with learning disabilities and epilepsy when compared with people with epilepsy who do not have learning disabilities?

This question has already been considered in Chapter 7.2 and no primary studies were identified that answered this question.

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

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

DeToledo 2002[429]

'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.[429]

14.4 Are there difficulties in doing investigations in this group?

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

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

245. In the child or young person presenting with epilepsy and learning disability, investigations directed at determining an underlying cause should be undertaken. [2004]

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.

14.4.1 Are there a) difficulties in conducting investigations (EEG; neuroimaging); b) difficulties in interpreting investigations (EEG; neuroimaging) in people with learning disability and epilepsy when compared with people with epilepsy who do not have learning disabilities?

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Brodtkorb 1994 [430]

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

Consensus guideline recommendations

Working group of the International Association of the Scientific Study of Intellectual Disability 2001 [427]

Kerr and colleagues recommended that:

- Facilities should be available for imaging under general anaesthesia.

14.5 What are the main factors to assess when making a care plan for an individual with learning disabilities and epilepsy?

246. In making a care plan for a child, young person or adult with learning disabilities and epilepsy, particular attention should be paid to the possibility of adverse cognitive and behavioural effects of AED therapy. [2004]

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

Evidence statements

There is no evidence to suggest that different antiepileptic drugs should be used for those with learning disabilities than for those without learning disabilities. (NICE)

People with learning disabilities and epilepsy are at increased risk of adverse cognitive or behavioural side effects from AEDs. (IV)

14.6 Pharmacological management of people with epilepsy and learning disabilities

14.6.1 Introduction

There is no evidence to suggest that epilepsy in the learning disabled population requires any different consideration with regard to treatment compared to those without learning disability. One could argue however, they may be more susceptible particularly to cognitive side effects of anticonvulsant medication. Further, they may be disadvantaged in their management by lack of self-advocacy.

14.6.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews.

For this review we included adults and children with learning disabilities and epilepsy. People with Lennox-Gastaut syndrome were excluded from this evidence review and were reported in a separate evidence review (see section 10.7).

14.6.3 Matrix of the evidence

We searched for RCTs comparing the effectiveness of different pharmacologcial interventions for adults and children with epilepsy and learning disabilities. The following interventions were included in our search; pregabalin, zonisamide, lacosamide, lamotrigine, gababentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenytoin, phenobarbital, clobazam, felbamate, acetazolamide, sodium valproate, primidone and carbamazepine. We looked for any RCT studies that compared the effectiveness of two or more of these treatments (or placebo).

Below is a matrix showing where evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo																		
Pregabalin																		
Zonisamide																		
Lacosamide																		
Lamotrigine																		
Gabapentin					1[431]													
Oxcarbazepine																		
Tiagabine																		
Levetiracetam																		
Topiramate	1[432]																	
Vigabatrin																		
Phenytoin																		
Phenobarbital																		
Clobazam																		
Felbamate																		
Acetazolamide																		
Sodium evaporate																		
Primidone																		
Carbamazepine																		
	Pla	PRE	ZNS	LCS	LTG	GBP	OXC	TGB	LEV	TPM	VGB	PHT	PBT	CLB	FBM	ACT	VPA	PRM	CBZ

Placebo (Pla)	Pregabalin (PRE)	Zonisamide (ZNS)	Lacosamide (LCS)	Lamotrigine (LTG)	Gabapentin (GBP)
Oxcarbazepine (OXC)	Tiagabine (TGB)	Levetiracetam (LEV)	Topiramate (TPM)	Vigabatrin (VGB)	Phenytoin (PHT)
Phenobarbital (PBT)	Clobazam (CLB)	Felbamate (FBM)	Acetazolamide (ACT)	Sodium valproate (VPA)	Primidone (PRM)
Carbamazepine (CBZ)					

14.6.3.1 Topiramate as adjunctive therapy versus placebo

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non- significant results

For adults and children with epilepsy and learning disabilities, there was no significant difference for the proportion of participants achieving at least 50% reduction in seizure frequency between topiramate adjunctive therapy and placebo. (VERY LOW QUALITY)

Adverse events – statistically significant results

For people with epilepsy and learning disabilities, significantly more patients had the following adverse events with topiramate adjunctive therapy compared to placebo:

- anorexia, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)
- somnolence, however there is uncertainty over the magnitude of the clinical effect. (LOW QUALITY)

Adverse events – statistically non-significant results

There was no significant difference for the proportion of participants that withdrew due to adverse events between topiramate adjunctive therapy and placebo. (VERY LOW QUALITY)

There was no significant difference between topiramate adjunctive therapy and placebo for the incidence of:

- accidental injury (VERY LOW QUALITY)
- asthesia (VERY LOW QUALITY)
- hostility (VERY LOW QUALITY)
- infection (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- abnormal gait (VERY LOW QUALITY)
- convulsions (VERY LOW QUALITY)
- nervousness. (VERY LOW QUALITY)

Quality of life- statistically non-significant results

No significant difference was found between topiramate adjunctive therapy and placebo on the following domains of quality of life:

- seizures (VERY LOW QUALITY)

- drugs (VERY LOW QUALITY)
- daily life (VERY LOW QUALITY)
- severity (VERY LOW QUALITY)
- side effects (VERY LOW QUALITY)
- behaviour (VERY LOW QUALITY)
- mood (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive topiramate to placebo in a population of patients with learning disabilities was identified.

Outcomes with no evidence

There were no studies that reported:

- seizure freedom
- time to first seizure
- time to exit/withdrawal

14.6.3.2 Gabapentin adjunctive therapy versus lamotrigine adjunctive therapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health economics

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

No significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of seizure free participants. (VERY LOW QUALITY)

No statistically significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of participants experiencing at least a 50% reduction in seizure frequency. (VERY LOW QUALITY)

Adverse events-statistically non-significant results

For people with learning disabilities, no statistically significant difference was found between gabapentin adjunctive therapy and lamotrigine adjunctive therapy for the proportion of participants withdrawn due to adverse events. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing adjunctive gabapentin to adjunctive lamotrigine in a population of patients with learning disabilities was identified.

Outcomes with no evidence

There were no studies that reported:

- withdrawal due to lack of efficacy
- time to first seizure
- time to exit/withdrawal of allocated treatment
- incidence of adverse events
- cognitive outcomes
- quality of life outcomes.

14.6.4 New recommendations and link to evidence

Recommendation	**248. Enable children, young people and adults who have learning disabilities, and their family and/or carers where appropriate, to take an active part in developing a personalised care plan for treating their epilepsy while taking into account any comorbidities. [new 2012]**
Relative values of different outcomes	The management of epilepsy in this patient group is no different than from a general epilepsy population. As for children, young people and adults without learning disabilities, seizure freedom, a reduction of seizures and avoidance of adverse effects are important outcomes. There was no evidence to suggest that efficacy of drugs differs for this population.
Trade off between clinical benefits and harms	Given the individual's complex co-morbidities, adults and children with learning disabilities and their family/carers could contribute actively to the establishment of setting priorities personalised to individual needs.
Economic considerations	The GDG considered that extra time may be required to implement this recommendation, but that personalised care plans for this group of patients may help improve the long- term outcomes of treatment and may ultimately reduce the need for hospital admissions, outpatient appointments and GP consultations. Outcomes may be improved as choice of drug and dose can be tailored more successfully to the patient, thereby reducing risk of discontinuation due to intolerable side effects. The GDG considered it likely to be a cost-effective use of resources, although no evidence is available.
Quality of evidence	This recommendation was based on GDG expertise.
Other considerations	GDG view is that this patient group has traditionally received sub-optimal care, and less access to specialist epilepsy services.

Recommendation	**249. Ensure adequate time for consultation to achieve effective management of epilepsy in children, young people and adults with learning disabilities. [new 2012]**
Relative values of different outcomes	The management of epilepsy in this patient group is no different than from a general epilepsy population. As for children, young people and adults without learning disabilities, seizure freedom, a reduction of seizures and adverse effects are important outcomes. There was no evidence to suggest that efficacy of drugs differs for this population, however, the GDG opinion was that importance is placed on cognitive and behavioural effects of AEDs as it may be more difficult to assess and treat in this population.
Trade off between clinical benefits and harms	Communication with the patient and the carer may be more challenging and it may take longer during the consultation to monitor any side effects and optimise drug management, particular considering issues that may arise under the Mental Capacity Act (2005).
Economic considerations	The GDG considered that additional time may be required to appropriately assess and manage this group of patients, but that it is likely to represent a cost-effective use of resources. Optimising their treatment is likely to improve their outcomes and may result in fewer hospital admissions, outpatient appointments and GP consultations.
Quality of evidence	This recommendation was based on GDG expertise.
Other considerations	GDG view is that this patient group has traditionally received sub-optimal care, and less access to specialist epilepsy services.

Recommendation	**250. Do not discriminate against children, young people and adults with learning disabilities, and offer the same services, investigations and therapies as for the general population. [new 2012]**
Relative values of different outcomes	The management of epilepsy in this patient group is no different than from a general epilepsy population. As for children, young people and adults without learning disabilities, seizure freedom, a reduction of seizures and adverse effects are important outcomes.
Trade off between clinical benefits and harms	GDG view is that this patient group has traditionally received sub-optimal care, and less access to specialist services.
Economic considerations	None.
Quality of evidence	This recommendation was based on GDG expertise.

Other considerations	GDG view is that this patient population has traditionally received sub-optimal care, and less access to specialist epilepsy services.

14.6.5 Is epilepsy more difficult to treat in people with learning disabilities?

251. Every therapeutic option should be explored in children, young people and adults with epilepsy in the presence or absence of learning disabilities. [2004]

Evidence statements

Remission rates for people with learning disabilities and epilepsy are lower than those for people with epilepsy who do not have learning disabilities. (IIb)

In community based studies of children with epilepsy and learning difficulties a significant (39-40%) proportion achieve remission. (IIb)

14.6.6 Likelihood of remission of seizures

Details

Only studies of prognosis that used a community sample of participants were included so as to avoid referral bias.

Secondary evidence

No systematic reviews were identified.

Primary Papers

Airaksinen 2000[433]

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.[433]

Annegers 1979[434]

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).[434]

Brorson 1987[435]

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%.[435]

Goulden 1991[436]

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.[436]

Sillanpaa 1975[437]

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.[437]

14.7 What are the additional management issues in people with learning disabilities?

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

253. All children, young people and adults 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 child, young person or adult are balanced with the role of the carer. [2004]**

Evidence statements

Mortality rates are higher in people with learning disabilities and epilepsy than those for people with epilepsy who do not have learning disabilities. However, epilepsy is not the major cause of death in this group. (IIb)

Management issues that are viewed as important by healthcare professionals and carers are:

- *Concerns about seizures and their impact on individuals with epilepsy and learning disabilities and their carers;*

- *Concerns about treatment and its impact on individuals with epilepsy and learning disabilities and their carers;*
- *Concerns about how both the carer(s) and an individual with epilepsy and learning disabilities can achieve a 'care balance';*
- *Concerns about the social impact for individuals with epilepsy and learning disabilities.(III)*

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

Details

Secondary evidence

No systematic reviews were identified.

Primary evidence

Brorson 1987[435]

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.[435]

Forsgren 1996[438]

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.[438]

Forssman 1970[439]

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).[439]

Nashef 1995[388]

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.[388]

14.7.2 What management issues in people with learning disabilities do healthcare practitioners and carers view as important?

Secondary evidence

No systematic reviews were identified.

Primary papers

Espie 2001[440]

The2001 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)[440]

15 Young people with epilepsy

15.1 Introduction

Adolescence is a period of transition from dependence to independence, when adolescents begin to adopt a multitude of new social and emotional roles and learn to cope with altered bodily functions. Adolescents with a chronic illness such as epilepsy are constantly struggling for independence. At the same time, their illness often keeps them tied physically, emotionally and financially to their families. Good management of this transition period by healthcare professionals is vital to develop and maintain the self-esteem and confidence of the adolescent with epilepsy.[441]

15.2 Is a different approach to management required in adolescence?

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

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

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

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

Evidence statement

No studies were identified which tested the effectiveness of interventions (e.g., educational interventions) designed to increase adherence with healthcare professional's advice in young people with epilepsy.

Details

No systematic reviews of RCTs or RCTs of different processes of care for adolescents with epilepsy were identified.

15.3 What are the factors that affect adherence to treatment in adolescents with epilepsy?

Secondary evidence

One systematic review of adherence with medication in people with epilepsy was identified. Although this review did not focus only on adolescents, it found that being a teenager was associated with poor adherence with medication [151].

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.[151]

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

The studies reported in the above systematic review[151] 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.

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

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

Evidence statement

No studies were identified which compared outcomes for young people attending specialist teenage epilepsy as opposed to those attending 'routine' child or adult clinics.

Details

Appleton 1999[442]

In this personal practice paper, the authors proposed that a specialist service should be provided because teenagers feel uncomfortable or may feel it inappropriate to continue to attend paediatric services, and they are likely to remain on medication for a long period of time. They suggested that this could be sited within a specific clinic for teenagers.

Smith 2002[443]

This paper reports the experience of one specific teenager epilepsy clinic. It does not compare outcomes for adolescents attending specialist teenage epilepsy as opposed to those attending 'routine' child or adult clinics.

15.5 What are the special needs or information requirements of this group?

260. 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 chapter 12). [2004]

Evidence statements

There is little research available on the specific information needs of young people. (III)
Individuals with epilepsy require information on: Epilepsy in general; Diagnosis and treatment options; Medication and side effects; Seizures and seizure control; Injury prevention; Psychological issues; Social security; Driving and insurance; Employment; Prognosis; Life style and social issues. (III)

Secondary evidence

Couldridge 2001[372]

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 review[372] identified one paper that dealt specifically with the experiences of young people with epilepsy.

Wilde 1996[444]

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 elationships 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.[444]

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

261. The diagnosis and management of epilepsy should be reviewed during adolescence. [2004]

Evidence statements

No studies were identified which compared outcomes for young people having their diagnosis reviewed/revisited at their outpatient clinic appointment as opposed to those who did not have their diagnosis reviewed/revisited.

One uncontrolled case review found that 10% of young people attending such a clinic did not have a diagnosis of epilepsy and 22% were on an inappropriate AED. (III)

It is the opinion of respected authorities that the diagnosis and management of epilepsy should be revisited in this group. (IV)

A revisit is indicated on the following grounds: the differential diagnosis of a seizure in young people is wide and can include non-epileptic attack disorder, vasovagal attacks and migraine. (IV)

There is a need to classify the epilepsy syndrome to ensure optimum treatment and accurate prognosis. The choice and side effects of antiepileptic drugs (AEDs) need to be considered in the short and long term. (IV)

Secondary evidence
No systematic reviews of the literature that addressed the above question were identified.

Primary evidence

Appleton 1997[445]
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'.[445]

Expert evidence

Appleton 1999[442]
Appleton and Neville stated that the adolescent period was an important time to review the diagnosis of both epilepsy and the epilepsy syndrome, and to consider any underlying cause. Reasons included previous misdiagnosis, and particularly the potentially serious implications of misdiagnosis for employment, driving, and psychosocial health.

16 Older people

16.1 Pharmacological management of epilepsy in older people

16.1.1 Introduction

The elderly are a rapidly growing population. As a consequence, an increasing number are presenting with epilepsy, many the result of cerebrovascular disease. There is no evidence to suggest that seizures are any more resistant to medication than the younger population. However, the high rate of other illness and comedication, susceptibility to side effects (eg cardiac) as well as the aging brain, suggest they may require very specific consideration with regard to treatment choice. We have used the definition of 65 years or older however this is based on the cut-off point in the majority of the literature. It should be recognised that older people may mean something different clinically.

16.1.2 Methods of the evidence review

Please see section 2.8 for general methods underpinning the evidence reviews. For this review we included older people taking anti-epileptic drugs. We looked for data specifically on the incidence of adverse events (10% or above), cognitive effects and quality of life. Only validated measures of cognitive effect and outcomes relating to quality of life have been investigated for the purposes of this evidence review. The GDG decided that evidence on the effectiveness of the various drugs at reducing number of seizures was better examined by considering the data from general epilepsy population. This data can be found in other sections of the guideline.

16.1.3 Matrix of the evidence

We searched for RCTs comparing the tolerability of different pharmacologcial interventions for epilepsy in an older population. The interventions we included in our search were pregabalin, zonisamide, lacosamide, lamotrigine gabapentin, oxcarbazepine, tiagabine, levetiracetam, topiramate, vigabatrin, phenyoin, phenobarbital, clobazam, clonazepam, felbamate, acetazolamide, primidone, sodium valproate and carbamazepine. We searched for any RCT studies that compared the tolerability of two or more of these treatments (or placebo). Below is a matrix showing were evidence was identified. A box containing a figure indicates the number of studies that were found and that the evidence for this comparison has been reviewed in this chapter. An empty box indicates that no evidence was found. In this case, no section on this comparison is included in the chapter.

Placebo							
Carbamazepine							
Carbamazepine – sustained release							
Lamotrigine		3[446,447] [164]	2 [448-450]				
Sodium valproate							
Phenytoin					1 [451]		
Gabapentin		1[446]		1[446]			

	PCB	CBZ	CBZ -SR	LTG	VPA	PHT	GBP

PCB – placebo CBZ – carbamazepine CBZ-SR – carbamazepine sustained release

LTG – lamotrigine VPA – sodium evaporate PHT – phenytoin

GBP – gabapentin

16.1.3.1 Lamotrigine monotherapy versus carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy– statistically significant results

Significantly more participants on carbamazepine compared to lamotrigine had seizure freedom (MODERATE QUALITY).

Adverse events – statistically significant results

Significantly more participants on carbamazepine monotherapy compared to lamotrigine monotherapy withdrew due to adverse events (MODERATE QUALITY).

Significantly more participants on lamotrigine monotherapy compared to carbamazepine monotherapy had:

- incidence of tremor (LOW QUALITY)
- incidence of weight loss (MODERATE QUALITY)

Significantly more participants on carbamazepine monotherapy compared to lamotrigine monotherapy had an incidence of:

- death (LOW QUALITY)
- somnolence (MODERATE QUALITY)

Adverse events – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and carbamazepine monotherapy for incidence of:

- rash (VERY LOW QUALITY)
- asthenia (VERY LOW QUALITY)
- poor co-ordination (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)
- sedation (VERY LOW QUALITY)
- GI problems (VERY LOW QUALITY)

- weight gain > 4lbs (VERY LOW QUALITY)
- water retention (VERY LOW QUALITY)
- Nystagmus (VERY LOW QUALITY)
- Dysarthria (VERY LOW QUALITY)
- gait problems (VERY LOW QUALITY)
- change in mood or affect (VERY LOW QUALITY)
- cognitive disturbances. (VERY LOW QUALITY)

Outcomes with no evidence

There were no studies that reported quality of life outcomes.

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to carbamazepine monotherapy was identified.

16.1.3.2 Lamotrigine monotherapy versus sustained-release carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy for seizure freedom (VERY LOW QUALITY).

There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy for time to exit/withdrawal (due to any events). (VERY LOW)

Adverse events – statistically significant results

Significantly more participants on sustained-release carbamazepine monotherapy compared to lamotrigine monotherapy had withdrawal due to adverse events (LOW QUALITY).

Adverse events – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy for the incidence of:

- dizziness (VERY LOW QUALITY)
- rash/skin reaction (VERY LOW QUALITY)
- headache (VERY LOW QUALITY)

Cognitive outcomes – statistically non-significant results

There was no significant difference between lamotrigine monotherapy and sustained-release carbamazepine monotherapy on the changes in SEALS score.

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to sustained-release carbamazepine monotherapy was identified.

Outcomes with no evidence

There were no studies that reported quality of life outcomes.

16.1.3.3 Sodium valproate monotherapy versus phenytoin monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between sodium valproate monotherapy and phenytoin for seizure freedom.

Adverse events – statistically non-significant results

There was no significant difference between sodium valproate monotherapy and phenytoin monotherapy for:

- withdrawal due to adverse events (VERY LOW QUALITY)
- incidence of unsteadiness (VERY LOW QUALITY)
- incidence of sleepiness (VERY LOW QUALITY)
- incidence of tremor (VERY LOW QUALITY)
- incidence of edema (VERY LOW QUALITY)
- incidence of alopecia (VERY LOW QUALITY)
- incidence of depression (VERY LOW QUALITY)
- incidence of weight gain (VERY LOW QUALITY)
- incidence of cognitive function. (MODERATE QUALITY)

Cognitive events – statistically significant results

There was significant improvement in cancellation time test scores for phenytoin monotherapy compared to sodium valproate monotherapy at 6 months only.

Cognitive events – statistically non-significant results

There was no significant difference between sodium valproate monotherapy and phenytoin monotherapy for all other cognitive tests at 6 weeks, 3 months, 6 months and 1 year.

Cost-effectiveness

No economic evidence comparing sodium valproate monotherapy to phenytoin monotherapy was identified.

Outcomes with no evidence

There were no studies that reported quality of life outcomes.

16.1.3.4 Gabapentin monotherapy versus carbamazepine monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non-significant results

There was no significant difference between gabapentin monotherapy and carbamazepine monotherapy for seizure freedom (VERY LOW QUALITY).

Adverse events – statistically significant results

Significantly more participants on gabapentin monotherapy compared to carbamazepine monotherapy had an incidence of:

- weight gain > 4lbs (MODERATE QUALITY
- water retention. (MODERATE QUALITY)

Significantly more participants on carbamazepine monotherapy compared to gabapentin monotherapy for withdrawal due to adverse events (LOW QUALITY).

Adverse events – statistically non-significant results

No significant difference between gabapentin monotherapy and carbamazepine monotherapy for the incidence of:

- GI problems (VERY LOW QUALITY)
- weight loss (VERY LOW QUALITY)
- nystagmus (VERY LOW QUALITY)
- dysarthris (VERY LOW QUALITY)
- gait problems (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- sedation (VERY LOW QUALITY)
- change in mood or affect (VERY LOW QUALITY)
- cognitive disturbances (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- incidence of headaches (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing gabapentin monotherapy to carbamazepine monotherapy was identified.

Outcomes with no evidence

There were no studies that reported quality of life outcomes.

16.1.3.5 Lamotrigine monotherapy versus gabapentin monotherapy

Clinical evidence

For details on the clinical evidence please refer to Appendix N. For details on each paper identified in the literature search please refer to Appendix L.

Health Economic Evidence

No studies were identified in the economic literature search.

Evidence statements

Efficacy – statistically non- significant results

There was no significant difference between lamotrigine monotherapy and gabapentin monotherapy for seizure freedom (VERY LOW QUALITY).

Adverse events – statistically significant results

Significantly more participants on lamotrigine monotherapy compared to gabapentin monotherapy had a higher incidence of weight loss. (MODERATE QUALITY)

Significantly more participants on gabapentin monotherapy compared to lamotrigine monotherapy had:

- withdrawal due to adverse events (MODERATE QUALITY).
- incidence of weight gain > 4 lbs (MODERATE QUALITY)
- incidence of water retention (MODERATE QUALITY)

Adverse events – statistically non-significant results

No significant difference between lamotrigine monotherapy and gabapentin monotherapy for the incidence of:

- GI problems (VERY LOW QUALITY)
- hyponatremia (VERY LOW QUALITY)
- nystagmus (VERY LOW QUALITY)
- dysarthria (VERY LOW QUALITY)
- gait problems (VERY LOW QUALITY)
- tremor (VERY LOW QUALITY)
- sedation (VERY LOW QUALITY)
- change in mood or affect (VERY LOW QUALITY)
- cognitive disturbances (VERY LOW QUALITY)
- dizziness (VERY LOW QUALITY)
- headaches. (VERY LOW QUALITY)

Cost-effectiveness

No economic evidence comparing lamotrigine monotherapy to gabapentin monotherapy was identified.

Outcomes with no evidence

There were no studies that reported quality of life outcomes.

16.1.4 New recommendations and link to evidence

Recommendation	**262. Do not discriminate against older people, and offer the same services, investigations and therapies as for the general population. [new 2012]**
Relative values of different outcomes	Adverse effects of drugs and quality of life were considered the most important outcomes for this review as older people are more susceptible to side effects of drugs. Effectiveness of the drugs at reducing numbers of seizures is also important but is dealt with in the other seizure and epilepsy syndrome sections of this guideline.
Trade off between clinical benefits and harms	AED are associated with potentially more adverse side effects in this patient group. The reduction in seizures found in our other reviews is assumed to be similar for older people. The GDG considered that the benefit of reduction in seizures outweighed the adverse effects associated with drug treatment in the same way as it does for other people with epilepsy.
Economic considerations	There was no economic evidence but the GDG considered that treatment with AEDs would be cost-effective for older people just as it is for other people with epilepsy.
Quality of evidence	This recommendation was based on outcome data that was moderate to very low quality and GDG expertise.
Other considerations	The GDG wished to ensure that older people had optimal treatment and had the same opportunities as other adults to access treatments and specialist epilepsy services. The GDG were concerned that this is not necessarily current practice.

Recommendation	**263. Pay particular attention to pharmacokinetic and pharmacodynamic issues with polypharmacy and comorbidity in older people with epilepsy. Consider using lower doses of AEDs and, if using carbamazepine, offer controlled-release carbamazepine preparations. [new 2012]**
Relative values of different outcomes	Incidence of adverse events and cognitive outcomes were clinically important outcomes for this recommendation.
Trade off between clinical benefits and harms	Carbamazepine had significantly higher incidence of death and somnolence compared to lamotrigine but there was no significant difference between the two drugs when carbamazepine was in the sustained-release formulation. Significantly more participants on lamotrigine had weight loss when compared to gabapentin and carbamazepine and higher tremor compared to carbamazepine. Significantly more participants on gabapentin had weight gain and water retention when compared to lamotrigine and carbamazepine. The GDG considered that older people may have equivalent reduction in seizures with lower doses of AEDs and by reducing the dose, adverse effects can be minimalised. The GDG considered that older people are more likely to have additional co-morbidities and also be taking drugs for these co-morbidities than other adults. Drug interactions and co-morbidities may cause undesirable pharmacokinetic and pharmacodynamic issues. Whilst it will take some additional time during the consultation for health care professionals to consider co-morbidities and polypharmacy, the GDG considered that the benefits outweighed the risks of not doing this.
Economic considerations	No economic evidence was available to inform cost-effectiveness of AEDs in older people specifically. The GDG thought that the effectiveness of AEDs in this group is likely to be similar to other epilepsy populations and therefore cost-effectiveness was likely to be driven by the incidence of intolerable side effects causing withdrawal of treatment. The GDG also considered that this population may respond to lower doses of a number of AEDs which could reduce the burden of some side-effects as well as reduce overall costs.The additional consultation time taken to consider co-morbidities and polypharmacy was considered to be worthwhile in order to reduce the risk of adverse effects of drug interactions. Finally, controlled-release formulations of carbamazepine are not more costly than non-controlled-release carbamazepine.
Quality of evidence	The quality of the studies was generally good, however the drop-out rate was extremely high, with differences between groups which could bias results. As the differential drop-out was over 20% we conducted a sensitivity analysis to confirm whether the differential drop-out affected the recommendation. We tested the difference of using available case analysis compared to ITT analysis in studies where there was a high differential drop-out. The

	outcomes that changed by using available case analysis were seizure freedom (from statistically significant to non-significant), incidence of poor co-ordination (from non-statistically significant to statistically significantly higher in the carbamazepine arm) and incidence of dizziness (from non-statistically significant to statistically significantly higher in the carbamazepine arm). The results did not affect the recommendation which was based on adverse events rather than efficacy. More adverse events were found to be statistically significant from using available case analysis, which re-inforces the difference between carbamazepine and carbamazepine controlled-release formulations for older patients.
Other considerations	The GDG expertise supported this recommendation that carbamazepine controlled-release formulation has similar efficacy to carbamazepine, and has a better adverse effects profile, with avoidance of high peak concentrations. The GDG expressed the view that older people have not in general received adequate access to specialist services and there is a risk that they are receiving less than optimum treatment and poorer outcomes. They therefore thought it was important to make this recommendation to pay particular attention to choice of drug and dose for older people.

17 People from black and minority ethnic groups

17.1 Introduction

The UK has a sizeable black and minority ethnic population. It is important that the health needs of individuals with epilepsy from black and minority ethnic groups are researched and the research findings disseminated to promote equity of care. To date published research in this area has been limited and has focused on small prevalence studies in particular ethnic groups.[452]
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.

17.2 What are the information and service provision needs of people from black and minority ethnic groups?

264. Children, young people and adults 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 a person's needs are appropriately met. [2004]

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

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

Evidence statements

South Asians with epilepsy want information on all aspects of epilepsy, including treatment and side effects, and further sources of support, information, and advice. (III)

No other evidence was identified about the information needs of individuals with epilepsy and/or their carers in other black and minority ethnic groups in the UK.

Details

No evidence was found in the Medicines Alliance review[151] or the Couldridge review[372] relating specifically to minority ethnic groups. One primary source of evidence was identified.[453]

Ismail and colleagues 2003[453]

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).

18 The care process for people with epilepsy

18.1 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 is 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).

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

267. Children, young people and adults with epilepsy should have a regular structured review and be registered with a general medical practice. [2004]

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

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

270. Epilepsy specialist nurses (ESNs) should be an integral part of the network of care of children, young people and adults 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 child, young person or adult, families, carers and, in the case of children, others involved in the child's education, welfare and well-being. [2004]

271. Children, young people and adults with epilepsy should have an accessible point of contact with specialist services. [2004]

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

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)

18.2.1 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.[454]

Primary evidence
SUDEP 2002[18]
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 care 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.[18]

Clinical Standards Advisory Group (CSAG) 2000[11]
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.[455-459] 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).[456] 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% [456], 5%[455]) and the audit data were not disaggregated into adults and children.

18.2.2 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

18.2.2.1 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.[11,18] This could be achieved by a structured annual review.

Secondary evidence

No systematic reviews were identified.

Primary evidence

No randomised controlled trials were found evaluating the effectiveness of structured review in the care of people with epilepsy.

The study by Thapar and colleagues[454] was excluded as this evaluated the opportunistic use of a prompt and reminder card in general practice as opposed to structured annual review.

18.2.2.2 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.[11,460] The deployment of nurses trained in epilepsy care (specialist epilepsy nurses) working in primary care who could liaise with secondary care has been proposed.[461]

Secondary evidence

Bradley 2003[462]

A Cochrane review assessed the effectiveness of specialist epilepsy nurses compared to routine care. Any RCTs or quasi-randomised trials that compared specialist nurse interventions compared to routine or alternative care were included.

Three trials were included, one in general practice and two in a neurology centre. The three trials only included individuals aged 15 years or older.

The findings from the trial based in general practice are summarised here.

The Ridsdale RCT[463] (and the follow-up paper[464]) 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[462] was that participants in the intervention group were told that they would attend a 'neurology clinic', which may have been interpreted as specialist care. Potentially this belief may have improved outcomes over and above the effects of the intervention from the epilepsy specialist nurse. The study key outcome variables were knowledge of epilepsy, and depression and anxiety scores at six months (assessed by validated questionnaires given before and after the intervention) and the recording of key variables (driving; drug compliance; adverse drug effects; alcohol, and self help groups) extracted from the clinical records.

The authors reported an increase of advice recorded in the notes of people with epilepsy ($p<0.001$). They also found a significant decrease in the risk for depression at six months ($p=0.024$) in those individuals who had not experienced an epileptic seizure in the last six months ($p=0.03$). However, there was no significant difference between control and intervention groups in those who had experienced a seizure in the last six months ($p=0.44$).

In conclusion, this study did not show an improvement in any clinically important outcomes[465] 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.[462]

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.

18.3 What features of the care process in secondary and tertiary care lead to improved health outcomes for adults and children with epilepsy?

273. 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 person or clinician view the epilepsy as inadequately controlled. [2004]

274. Adults with well-controlled epilepsy may have specific medical or lifestyle issues (for example, pregnancy or drug cessation) that may need the advice of a specialist. [2004]

275. Children and young people should have a regular structured review with a specialist. [2004]

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

277. At the review, children, young people and adults should have access to: written and visual information; counselling services; information about voluntary organisations; epilepsy specialist nurses; timely and appropriate investigations; referral to tertiary services including surgery, where appropriate. [2004]

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

Evidence statements

There is a lack of good quality evidence of effectiveness of dedicated epilepsy clinics in secondary and tertiary care. (Ia)

There is some evidence that epilepsy specialist nurses improve clinically important outcomes such as knowledge, anxiety and depression for people with epilepsy in secondary and tertiary care. (III)

18.3.1 What evidence is there of the quality of care currently provided in secondary/tertiary care?

Details

Secondary evidence

No systematic reviews were identified that summarised the quality of care in the secondary and tertiary care settings.

Primary evidence

SUDEP report[18]

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.[18]

Clinical Standards Advisory Group (CSAG) report 2000[11]

Users' perspectives on care

The Clinical Standards Advisory Group was asked to advise on standards of NHS services for people with epilepsy. As part of the report, the experience of users was studied[466]. 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

CSAG[11] 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 2003[467]
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.[467]

Other primary evidence
Bradley 1999[468]
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.[468]

Reynders 2002[469]
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.[469]

18.3.2 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

18.3.2.1 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.[11,460]

Secondary Evidence
Bowley 2000[470]
In a recent narrative literature review of epilepsy in people with learning disabilities, no evidence of research in service delivery was identified.

Bradley 2003[471]
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 epilepsy[471].

18.3.2.2 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,[11,460] and detailed descriptions of the role have been proposed.

Secondary evidence
Bradley 2003[462]

A Cochrane review assessed the effectiveness of specialist epilepsy nurses compared to routine care. Any RCTs or quasi-randomised trials that compared specialist nurse interventions compared to routine or alternative care were included.
Three trials were included, one in general practice and two in neurology centres. The three trials only included adults aged 15 years or older. The two trials in neurology centres are presented below.

Ridsdale and colleagues assessed the effect of an epilepsy nurse specialist on newly diagnosed adults' knowledge of epilepsy, satisfaction with the advice provided, and psychological well-being[472]. The trial was assessed as of adequate quality. Individuals randomised to see the nurse specialist were significantly more likely to report that enough advice had been provided on most epilepsy-related topics compared with the control group. There were no significant differences in knowledge of epilepsy scores. However, there were significant differences in the group who, at baseline, had knowledge scores in the lowest quartile; those randomised to the nurse had higher knowledge scores (42.7 vs. 37.2; $p<0.01$). Compared with doctors, the nurse was highly rated for providing clear explanations.
The quality of the trial based in tertiary care[473] was assessed as unclear. There was no significant difference between the intervention and control group for seizure frequency, levels of anxiety and depression, social functioning, overall health status, or absence from work. However, there was an increase in knowledge in the intervention group ($p=0.035$), although there is some concern about the reliability of the scale used (EKP-G scale). This trial reported a significant decrease in outpatient clinic hospital attendances ($p<0.01$) and a non-significant decrease in GP consultations ($p=0.054$). The economic evaluation suggested that specialist epilepsy nurse care is cheaper than standard care, but there were several flaws. However, the review stated that there was no evidence to suggest that specialist nurses were more expensive[462].
The review concluded that, for both primary and secondary/tertiary care, there was no convincing evidence that specialist nurse services improve outcomes for people with epilepsy, but low baseline knowledge in individuals with newly diagnosed epilepsy may be improved.

Meads 2002[474]
Meads and colleagues reviewed the literature on both specialist epilepsy clinics compared to general neurology clinics and specialist nurses compared to usual care. Unlike the Cochrane reviews described above, study designs other than RCTs were included.
For epilepsy clinics, the evidence was of poor quality with poorly designed studies and a different case-mix between specialist clinics and general neurology clinics.
For specialist nurses, the evidence was of a higher quality but showed no differences regarding seizure frequency or seizure severity between those receiving care from specialist nurses or usual care. However, there was some evidence that incidence of depression was decreased (one study of three). There was good evidence to show that the process of care was improved and that user satisfaction was improved. The one RCT that compared quality of life showed no difference between the groups.
The results were summarised as:

- Epilepsy clinics showed no evidence of reduced seizure frequency or severity, no quality of life information and were more expensive.
- Epilepsy nurse services showed no evidence of reduced seizure frequency or severity, no effect on quality of life but were less expensive[474].

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

Health economics
Meads 2002[474]
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.[474]

18.4 What features of the care process in A&E lead to improved health outcomes for adults and children with epilepsy?

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

280. Children, young people and adults 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[ll] when an epileptic seizure is suspected or there is diagnostic doubt. [2004]

281. Protocols should be in place that ensure proper assessment in the emergency setting for children, young people and adults presenting with an epileptic seizure (suspected or confirmed). [2004]

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

18.4.1 Quality of care currently provided in and accident and emergency departments (A&E)

Details
A&E departments often provide care to people with epilepsy for various reasons. In one study,[475] 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 report[11]

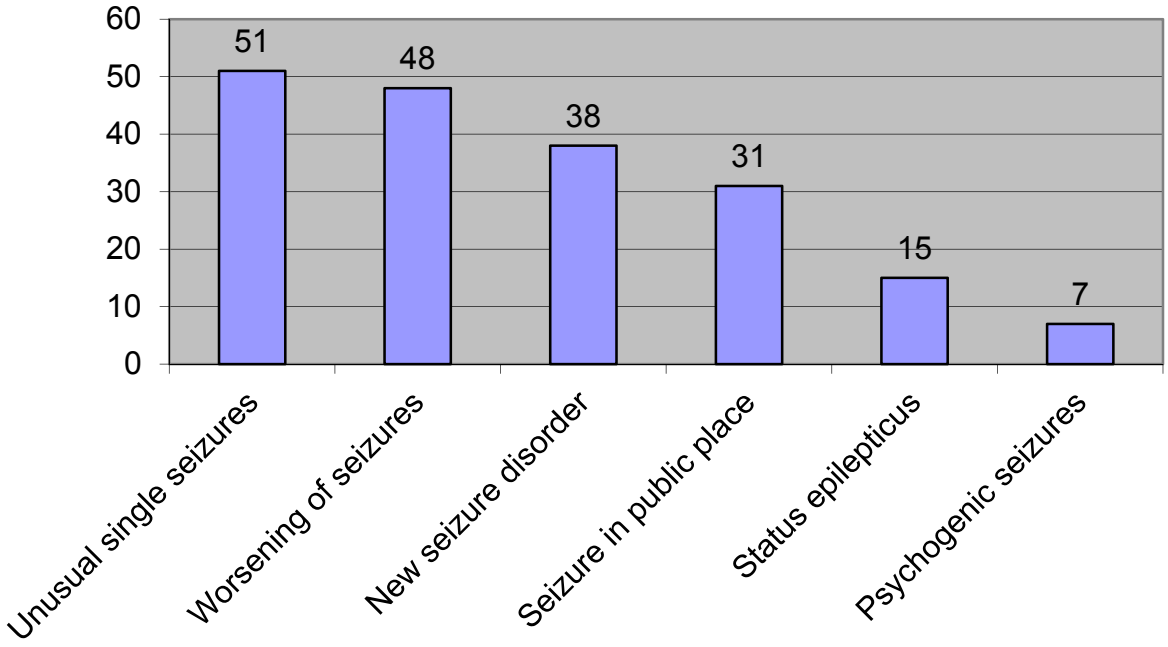
[ll] For adults , a specialist is defined throughout as a medical practitioner with training and expertise in epilepsy. For children and young people, a specialist is defined throughout as a paediatrician with training and expertise in epilepsy.

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 1998[476]
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.[476]

Reuber 2000[477]
Reuber and colleagues reviewed the A&E records of all adults attending the casualty department at St James's University Hospital with emergencies related to epilepsy between 1 April and 30 September 1998. Out of a total of 36 024 adults attending, 190 were emergencies relating to epilepsy.
A problem relating to a previously recognized seizure disorder was the commonest reason for attendance (see 18.1). Only 20% of attendances were for first seizures (38/190). Care was highly variable and often suboptimal. Descriptions of seizure semiology and examination findings were frequently deficient with only 59.4% (113 of 190) having a description recorded and 77.4% (147 of 190) having some form of neurological examination. Most who attended did not require any treatment with anticonvulsants in A&E. Only 19.5% (37 of 190) of cases received anticonvulsants acutely. Intravenous or rectal diazepam was invariably used as first-line treatment. Neurology Senior House Officers (SHOs) or registrars were only contacted about a minority of cases (19.5%, 37 of 190). 59% (112 of 190) of all individuals seen with emergencies relating to epilepsy were discharged home from A&E. 20% (3 of15) 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).[477]

Figure 3: Causes of attendance[477] 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.[478]

18.4.2 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.

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

18.5.1 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.

18.5.2 Do adults and children with epilepsy who are educated in self-management, when compared with those who do not, have better health outcomes?

282. Children, young people and adults with epilepsy and their families and/or carers should be empowered to manage their condition as well as possible. [2004]

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

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

285. Healthcare professionals should highlight the Expert Patients Programme (www.expertpatients.co.uk[mm]) to children, young people and adults with epilepsy who wish to manage their condition more effectively. [2004, amended 2012]

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 1990[479]

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 ($F(1,24)=4.18$, $p<0.05$).[479]

May 2002[379]
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

[mm] The web address has changed since the recommendation was published in 2004 and has been updated.

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.[379]

Lewis 1990[480] and Lewis 1991[481]

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 ($p<0.002$).[480]

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).[481]

Tieffenberg 2000[482]

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.[482]

19 Glossary

Absence Seizure	A seizure characterised by behavioural arrest associated with generalised spike wave activity on EEG.
Absolute risk reduction (Risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation.[483]
Adjunctive treatment	Where a medication is added to a first line AED for combination therapy.
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Aetiology	The cause or origin of a disease or disorder as determined by medical diagnosis.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Anti-epileptic drug (AED)	Medication taken daily to prevent the recurrence of epileptic seizures. Refer to Appendix K concerning the choice of drug, side effects and suitability to syndrome.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines Research and Evaluation (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org/). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Atonic seizure	A generalised seizure characterised by sudden onset of loss of muscle tone.
Attack	An episode in the course of an illness.

Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
BECTS	Benign epilepsy with centrotemporal spikes. An epilepsy syndrome of childhood (5-14 years) characterised by focal motor and/or secondarily generalized seizures, the majority from sleep, in an otherwise normal individual, with centrotemporal spikes seen on on EEG.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Borderline intelligence	Minimal IQ required to function normally and independently in the world.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Childhood absence epilepsy	An epilepsy syndrome with an age of onset of 4-9 years, characterised by frequent absence seizures associated with 3Hz spike wave activity on EEG.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.
Clinical presentation	The description of the history and presention of the clinical condition to the assessing medical team

Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.[483]
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.[483]
Conference proceedings	Compilation of papers presented at a conference.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the

	population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Convulsive status epilepticus (CSE)	When a convulsive seizure continues for a prolonged period (longer than 5 minutes), or when convulsive seizures occur one after the other with no recovery between. Convulsive status epilepticus is an emergency and requires immediate medical attention.
Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Credible interval	The Bayesian equivalent of a confidence interval.
Cross-over trial	A trial in which each of the study groups will receive each of the treatments, but in a randomised order: that is, they will start off in one arm of the trial, but will deliberately 'cross over' to the other arm(s) in turn (HTA).
Cryptogenic	Unknown cause.
CSWS	Continuous spike wave during slow sleep; an epilepsy syndrome of onset in children characterised by a plateau and regression of cognitive abilities associated with dramatic increase in spike wave activity in slow wave sleep (>85% of slow sleep). There may be few seizures at presentation.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Diplopia	Double vision.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.

Dravet syndrome	Previously known as severe myoclonic epilepsy of infancy. An epilepsy stndrome with onset in infancy, characterised by initial prolonged,typically lateralised, febrile seizures, subsequent development of multiple seizure types including myoclonic, absence, focal and generalised tonic clonic seizures, with developmental plateau or regression.
Drop-out	A participant who withdraws from a clinical trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effect size	This term is usually used in meta-analysis to denote treatment effect, or estimate of effect. It also refers to standardised mean difference (SMD), obtained by dividing the mean difference with the pooled standard deviation. This is the meaning usually referred to in GRADE.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Electro-encephalography (EEG)	An investigation that involves recording of the electrical activity of the brain. Electrodes are attached to standardised points on the individual's head with collodion. Recordings are usually taken across two points. for the role of EEG in diagnosis of epilepsy and epilepsy syndromes.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
Epilepsy	A condition where an individual is prone to recurrent epileptic seizures.
Epileptic seizure*	A transient occurrence of signs and/or symptoms, the result of a primary change to the electrical activity (abnormally excessive or synchronous) in the brain.
Epileptic Spasm	An involuntary muscle contraction of sudden onset.
Epilepsy syndromes*	Distinctive disorders identifiable on the basis of a typical age of onset, seizure types, specific EEG characteristics, and often other features. Identification of such has implications for treatment, management and prognosis.
Epileptic disease*	A pathologic condition causing epilepsy with a single specific, well-defined etiology. Thus progressive myoclonus epilepsy is a syndrome, but Unverricht-Lundborg is a disease.

Epileptic encephalopathy*	A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Focal ceizures	Seizure which originates 'within networks limited to one hemisphere, discretely localised or more widely distributed. Replaces the terms partial seizures and localization-related seizures.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Generalised seizure	A seizure which originates in, and rapidly engages, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures but do not necessarily include the entire cortex (ILAE 2010)

Generalised tonic-clonic seizure	A seizure of sudden onset involving generalised stiffening and subsequent rhythmic jerking of the limbs, the result of rapid widespread engagement of bilateral cortical and subcortical networks in the brain.
Genetic (with reference to epilepsy)	The epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder (ILAE 2010)
Girls of child-bearing age	Girls who have entered menarche and who are menstruating
Gold standard	See 'Reference standard'
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of limited resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypothesis	A supposition made as a starting point for further investigation.
Ictal phenomenology	Description or history of ictal events (seizures).
Idiopathic	A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms.These are presumed

	to be genetic in aetiology and are usually age dependent (ILAE 2001).
Idiopathic epilepsy syndrome*	A previously used term for a syndrome that involves 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. It is no longer recommended that this terminology is used.
Idopathic generalised epilepsy	A well-defined group of disorders characterised by typical absences, myoclonic and generalised tonic-clonic seizures, alone or in varying combinations in otherwise normal individuals. The EEG is also characteristic demonstrating a distinct pattern of generalised polyspike wave discharges and/or generalised spike wave. Of presumed genetic aetiology. The new classification of the ILAE 2010 suggeste terminology should change to 'genetic generalized epilepsy'.
Idiosyncratic	Physical or behavioural characteristic that is personal to that individual.
International League Against Epilepsy (ILAE)	International League Against Epilepsy. The ILAE is a global, professional and non-profit international organisation and a non-governmental organisation with an official relationship with the WHO (World Health Organisation). The ILAE's objectives are: to advance and disseminate knowledge about epilepsy (having developed guidelines for the classification of epilepsy and the design of investigative trials); to promote research, education and training; and to improve overall patient care.
Imprecision	Imprecision is one of the quality elements considered under the GRADE system. Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. $ICER=(Cost_A – Cost_B) / (Effectiveness_A – Effectiveness_B)$.
Inconsistency	Inconsistency is one of the elements of quality considered under the GRADE system. Inconsistency refers to the unexplained heterogeneity in the results observed.

Index	In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.
Indirectness	Indirectness is one of the elements of quality considered under the GRADE system. Indirectness of evidence refers to the difference in study population, intervention, comparator and outcomes between the available evidenced and the clinical question or population addressed in the guideline recommendations.
Indication (specific)	The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).
Infantile spasms	A specific seizure type presenting in the first year of life, most commonly between 3 and 9 months of age. Spasms are brief axial movements lasting 0.2-2 seconds, most commonly flexor in nature, involving flexion of the trunk with extension of the upper and lower limbs. They are occasionally referred to as 'salaam seizures'.
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Intermediate outcomes	Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study.
Internal validity	The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Juvenile absence epilepsy	An epilepsy syndrome with an age of onset of 9-13 years characterised by absence seizures associated with 3-4Hz spike wave on EEG. Generalised tonic-clonic seizures may occur.
Juvenile myoclonic epilepsy	An epilepsy syndrome with an age of onset of 5-20+years (peak, 10-16), characterised by myoclonic seizures which most commonly occur soon after wakening. Absence and generalised tonic-clonic seizures may occur in between 50 and 80% of people. EEG demonstrates 3-6Hz generalised polyspike and wave activity, with photosensitivity in >30%.
Ketogenic diet	A specific diet which is high in fats but low in carbohydrates and protein.

Landau-Kleffner Syndrome	A very rare epilepsy syndrome with an age of onset of 3-6 years characterised by loss of language (after a period of normal language development) associated with an epilepsy of centrotemporal origin, more specifically bitemporal spikes on EEG with enhancement in sleep or CSWS.
Late-onset childhood occipital epilepsy (Gastaut type)	Epilepsy with an age of onset in mid-childhood to adolescence with frequent brief seizures characterised by initial visual hallucinations, ictal blindness, vomiting and post-ictal headache. EEG typically shows interictal occipital spikes attenuated by eye opening.
Length of stay	The total number of days a participant stays in hospital.
Lennox-Gastaut syndrome	An epilepsy syndrome with an age of onset of 3-10 years characterised by multiple seizure types (including atonic, tonic, tonic-clonic and atypical absence seizures), cognitive impairment and specific EEG features of diffuse slow spike and wave (<2Hz) as well as paroxysmal fast activity (10 Hz or more) in sleep.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio (LR)	The ratio of the probability that a person with a condition has a specified test result to the probability that a person without the condition has the same specified test result. For positive test results, this is referred to as "Likelihood ratio positive", LR+. For negative test result, this is known as "Likelihood ration negative", LR-.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Marketing authorisation	An authorisation that covers all the main activities associated with the marketing of a medicinal product. Medicines that meet the standards of safety, quality and efficacy set by the Medicines and Healthcare products Regulatory Agency (MHRA) are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold.
Markov model	A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Minimal important difference (MID)	This is the smallest change which can be recognised by a patient as being clinically significant
Monotherapy	Use of a single drug in treatment.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Myoclonic-astatic epilepsy (MAE)	Myoclonic-astatic epilepsy or Doose syndrome. An epilepsy syndrome with an age of onset of 18-60 months, characterised by different seizure types with myoclonic and myoclonic-astatic seizures seen in all, causing children to fall. The EEG shows generalised spike/polyspike and wave activity at 2-6 Hz.
Myoclonic seizures	Sudden brief (<100ms) and almost shock-like involuntary single or multiple jerks due to abnormal excessive or synchronous neuronal activity and associated with polyspikes on EEG.
Narrative summary	Summary of findings given as a written description.
Negative likelihood ratio (LR)	The ratio of the probability that a person with a condition has a negative test result to the probability that a person without the condition has negative test result. Likelihood ratio negative, LR - = (1-sensitivity)/specificity See “likelihood ratio” and “positive likelihood ratio”.
Negative predictive value (NPV)	Proportion of patients with a negative test result who do not have the disease = TN/(FP+TN).
Neurological deficit	A deficiency or impairment of the nervous system.
Non-convulsive status epilepticus	A change in mental status or behaviour from baseline, associated with continuous seizure activity on EEG, that is also seen to be a change from baseline.
Non-epileptic attack disorder (NEAD)	A disorder characterised by episodes of change in behaviour or movement, not caused by a primary change in electrical activity of the brain. Movements are varied, and the attacks can be difficult to differentiate from epileptic seizures. Refer to Appendix A for the differentiations of epileptic attacks from NEAD and its subgroups.
Nystagmus	Involuntary rapid movement (horizontal, vertical, rotatory, or mixed) of the eyeballs.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator

	observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Older people	We have used the definition of 65 years or older however this is based on the cut-off point in the majority of the literature.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Panayiotopolous syndrome	Epilepsy syndrome presenting in early childhood (mean 4- 7 yrs) with rare seizures which are prolonged. Characterised by autonomic features including vomiting, pallor, and sweating followed by tonic eye deviation, impairment of consciousness with possible evolution into secondary generalisation. Prognosis is excellent and treatment often unnecessary.
Parasomnia	Any behavioural abnormality associated with sleep. For example, headbanging/confusional arousal/REM sleep disorder – night terrors.
Patient reported outcomes (PRO) or patient reported outcomes measures (PROMS)	These terms covers a whole range of potential types of measurements (e.g. symptoms severity or bother, health related quality of life, satisfaction with treatment) but is used specifically to refer to questionnaires designed to obtain the perspective of the patient rather than the perspective of clinicians or carers. PRO data may be collected via self-administered questionnaires completed by the patient themselves or via interviewer-administered questionnaires. These questionnaires should be developed and validated before use.
Pharmacokinetics	The way in which a drug is processed by the body, influencing absorption, metabolism, distribution and excretion.

Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Placebo	An inactive but physically identical medication or procedure used as a comparator in controlled clinical trials. Also sometimes referred to as a 'dummy' treatment.
Placebo effect	A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.
Polypharmacy	Multiple different drugs used in a patient's treatment, which could include AEDs.
Polytherapy	Two or more medications used in combination therapy. The guideline specifically refers to AEDs.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product. A drug may be "licensed" for several conditions. When a drug is referred to as "unlicensed" for a particular indication, that means that the drug may have a marketing authorisation for other conditions, but not for the condition discussed. This is also known as "off label" use.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective.*
Provocation techniques	Methods used to provoke seizures such as hyperventilation, photic stimulation, sleep deprivation and withdrawal of medication.
Psychogenic non-epileptic seizure (PNES)	A type of non-epileptic attack disorder (NEAD). See NEAD.
Puerperium	The time after childbirth, lasting approximately 6 weeks, during which the anatomic and physiologic changes brought about by pregnancy resolve and a woman adjusts to the new or expanded responsibilities of motherhood and non-pregnant life.
Qualitative research	Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.

Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Reflex epilepsy syndromes*	Syndromes in which all epileptic seizures are precipitated by particular 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. This can occur in both convulsive and non-convulsive status epilepticus.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective.*

Secondarily Generalised Seizure	Now referred to as a 'focal seizure evolving to a bilateral convulsive seizure' (ILAE 2010).
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity analysis (SA)	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Simple and complex partial epileptic seizures*	These terms are no longer recommended. They have been generally replaced with the single word, focal'. Focal seizures should include a clear description of impairment of consciousness.
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.
Specific cognitive dysfunction	Defined as performing below the 5th centile for one or more on the following tests of cognitive function 1.'visuoconstructive' score of WIPPSI 2. auditory phonemic score of ITPA 3. comprehension score of NEPS
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be

	missed.
Status epilepticus (convulsive) (CSE)	See convulsive status epilepticus above.
Sudden unexpected (or unexplained) death in epilepsy (SUDEP)	Sudden, unexplained, 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. *Provided by Nashef L. Sudden unexpected death in epilepsy: Terminology and definitions. Epilepsia 1997;38:S20-S22.*
Symptomatic epilepsy syndrome*	Previously used term that refers to a syndrome in which the epileptic seizures are the result of one or more identifiable structural lesions of the brain. This terminology is no longer recommended for use. See table 9.7.
Syncope (vasovagal syncopal attack)	A brief lapse in consciousness caused by transient reduction in blood flow to the brain. May be caused by many different factors, including emotional stress, vagal stimulation, vascular pooling in the legs, diaphoresis, or sudden change in environmental temperature or body position.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Teratogenic	An event or process which interferes with normal prenatal development, causing the development of one or more developmental abnormalities in the fetus.
Tertiary Epilepsy Specialist	A tertiary epilepsy specialist is an adult or paediatric neurologist who devotes the majority of their working time to epilepsy, who is working in a multidisciplinary tertiary referral centre with appropriate diagnostic and therapeutic resources and is subject to regular peer review
Tertiary centre	Specialist care delivery unit, to which individuals may be referred from secondary care.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Tonic seizures	An epileptic seizure characterised by abrupt generalised muscle stiffening possibly causing a fall. The seizure usually lasts less than a minute and recovery is rapid.

Tonic-clonic seizure	An epileptic seizure characterised by initial generalised muscle stiffening, followed by rhythmical jerking of the limbs, usually lasting a few minutes. The person may bite their tongue and may be incontinent. They may feel confused or sleepy afterwards, and take a while to recover fully.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Wash-out period (for cross-over studies)	A stage in a crossover trial after the first treatment is withdrawn, but before the second treatment is started. The washout period allows time for any active effects of the first treatment to wear off before the next phase begins.
West syndrome	An epilepsy syndrome with an age of onset in the first year of life (peak, 3-9months) characterised by infantile spasms and an EEG pattern described as hypsarrhythmia. Many children also show developmental plateau at presentation.

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

*Definitions from ILAE Task Force on Classification (updated 2010)

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