Appendix A: Summary of evidence from surveillance

2018 surveillance of *Epilepsies: diagnosis and management* (2012) NICE guideline CG137

Summary of evidence from surveillance

### 1.1 Principle of decision making

Recommendations in this section of the guideline

1.1.1 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]

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**Principle of decision making**

**2018 surveillance summary**

No relevant evidence was identified.

**2014 surveillance summary**

No relevant evidence was identified.

**Topic expert feedback and additional information**

No topic expert feedback was relevant to this evidence.

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Initial intelligence gathering identified NICE guideline CG138 *Patient experience in adult NHS services* which covers the components of a good patient experience.

**Impact statement**

NICE guideline CG138 provides a set of recommendations on making sure that adults using NHS services have the best possible experience of care, as such NICE guideline CG137 should cross-refer to the guideline; and consideration should be given to withdrawing the current recommendation.

**New evidence identified that may change current recommendations.**
1.2 Coping with epilepsy

Recommendations in this section of the guideline

1.2.1 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]

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

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

1.2.4 Healthcare professionals should highlight the Expert Patients Programme* 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.

Coping with epilepsy

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Impact statement
The evidence supports current recommendation content to offer structured self-management plans.

New evidence is unlikely to change guideline recommendations.

1.3 Information

Recommendations in this section of the guideline

1.3.1 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.

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

1.3.3 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]

1.3.4 If children, young people and adults, and their 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). [2004]

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

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

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

1.3.8 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]

1.3.9 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]

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

1.3.11 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]

1.3.12 The risk of SUDEP can be minimised by:
   - optimising seizure control
   - being aware of the potential consequences of nocturnal seizures. [2004]

1.3.13 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]

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

Information

2018 surveillance summary

A Cochrane review evaluating the effectiveness of interventions in preventing Sudden Unexpected Death in Epilepsy (SUDEP) in people with epilepsy, only found 1 case-control study at serious risk of bias (n=154 cases of SUDEP and 616 controls). The study showed that nocturnal supervision, a supervising person sharing the same bedroom, or taking special precautions such as using a listening device have a protective effect against SUDEP, which is independent of seizure control. [2]

2014 surveillance summary

A systematic review and meta-analysis of 112 RCTs (21,224 participants) investigating whether receiving effective doses of anti-epileptic drugs (AEDs) reduced the risk of sudden unexpected death in epilepsy (SUDEP) in patients with refractory epilepsy found that compared with patients allocated to placebo, patients assigned to effective doses of AEDs had a lower incidence of definite and probable SUDEP and a reduced frequency of all causes of death. The evidence suggests that adults with refractory epilepsy are at lower risk of SUDEP if they are treated with effective doses of adjunctive AEDs. [3]

Topic expert feedback


A topic expert said that parents frequently ask about overnight monitoring of their child’s seizures. There are now many seizure detection devices available, some of which (Emfit monitor, epilepsy smartwatches) have undergone clinical testing (no references provided). However, there is no guidance on what to advise parents regarding monitoring their child overnight.

Impact statement

This section of the guideline that relates to SUDEP should be updated. The Cochrane review reported that there was ‘very low-quality evidence of a preventative effect for nocturnal supervision against SUDEP’, the
current recommendation notes the importance of being aware of the ‘potential consequences of nocturnal seizures’ but does not mention nocturnal supervision, while the evidence is very low quality, this may have an impact on the recommendation. The practice guideline is in line with current recommendations, but also highlights additional details such as recommending that clinicians inform people with epilepsy that seizure freedom, particularly freedom from generalized tonic-clonic seizures, is strongly associated with decreased risk of SUDEP.

New evidence identified that may change current recommendations.

1.4 Following a first seizure

Recommendations in this section of the guideline

1.4.1 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]

1.4.2 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]

1.4.3 The information that should be obtained from the adult and/or family or carer after a suspected seizure is contained in appendix D. [2004]

1.4.4 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 D. [2004]

1.4.5 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]

1.4.6 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]

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

1.4.8 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]

1.4.9 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]

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

** Following a first seizure

** 2018 surveillance summary
No relevant evidence was identified.

** 2014 surveillance summary
No relevant evidence was identified.

** Topic expert feedback
No relevant evidence was identified.

** Impact statement
No new information was identified at any surveillance review. The absence of new evidence indicates that there is no need to update this section of the guideline.

No new evidence. Recommendations are unlikely to change.

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** 1.5 Diagnosis

Recommendations in this section of the guideline

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

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

1.5.3 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]

1.5.4 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]

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

1.5.6 It may not be possible to make a definite diagnosis of epilepsy. If the diagnosis cannot be clearly established, further investigations (see section 1.6) and/or referral to a tertiary epilepsy specialist (see recommendation 1.10.2) should be considered. Follow-up should always be arranged. [2004]

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

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

* In this recommendation, 'centre' has been replaced with 'specialist' for consistency across recommendations.
Diagnosis

2018 surveillance summary

Clinical decision rules
A systematic review examined use of clinical decision rules (CDRs) in epilepsy. Five studies considered to be moderate quality were included; meta-analysis of two validated CDRs found high initial accuracy levels with sensitivity of approximately 80% of above, which "tended to diminish significantly" in validation studies. Pooled estimates of sensitivity and specificity showed wide 95% confidence and prediction intervals which may restrict their value in clinical practice. [4]

Questionnaires/psychometric tests
A systematic review of 9 studies focused on use of screening questionnaires to diagnose epilepsy in adult subjects compared with clinical evaluation. The authors noted that studies had a high risk of bias. In individuals with a lifetime history of epilepsy ranges of 81.5-100% for sensitivity and 65.6-99.2% for specificity were reported. In individuals with active epilepsy sensitivity and specificity ranged from 48.6-100% and 73.9-99.9%, respectively. [5]

A retrospective study with patients with either psychogenic nonepileptic seizures (PNES) (n=30) or epilepsy (n=30) matched on age and sex, assessed the value of a review of system (ROS) questionnaire in distinguishing between seizure groups. The questionnaire consists of 10 general yes/no questions about the presence or absence of any abnormality in body systems. The mean (+/- SD) ROS response for the presence of any abnormality was 2.43 (+/-1.33) for the PNES group and 1.50 (+/-0.94) for the epilepsy group (p=0.01). A cut-off point of three positive ROS was able to differentiate the two conditions (p=0.01; OR: 6, 95% confidence interval: 1.48-24.29). The authors concluded that "multiple complaints in the ROS questionnaire argues in favour of PNES compared with epilepsy". [6]

A retrospective study of 595 patients with either ES, PNES, physiologic nonepileptic seizure-like events (PSLE), mixed PNES plus ES or inconclusive monitoring assessed frequency of "positive complaints" on ROS questionnaires as an early screening tool for distinguishing between seizure groups. Binominal regression showed some patient groups (PNES, mixed PNES and ES) had a significantly greater number of symptoms compared with PSLE or isolated ES. Multivariate logistic regression, controlling for sex and the number of medical comorbidities demonstrated that the prospective accuracy to differentiate PNES from ES was not significantly higher than assuming that all patients had ES (76% versus 70%, p>0.1). The authors concluded that the consistency of ROS responses was 'neither accurate nor specific enough to be used solely as an early screening tool for PNES'. [7]

A retrospective study of 44 patients with either PNES or ES assessed following completion of a standardised ROS to assess the value of multiple complaints as a marker of PNES. Multivariate analysis of covariance showed a significantly greater number of complaints in patients with PNES compared with ES in the ROS questionnaire, whereby a threshold level of 17% of positive complaints resulted in sensitivity and specificity values of 85% and 78% respectively for differentiating between PNES and ES. [8]

A study used the Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF) to differentiate between seizure types in 169 individuals with either epileptic seizures (ES) or PNES. In PNES, the odds of scale elevations for certain behaviours (negative mood, suicidal ideation and somatic concerns) were 2 to 5 times more likely. Gender differences were found with female PNES patients having 3-6 times greater odds of such scale elevations, while male PNES patients had odds of 5-15 times more likely. Positive and negative predictive values varied between 53.66-84.62% and 47.52-90.91% respectively and false discovery and omission

rates ranged from 15.38- 50% and 9.09- 52.47% respectively for scales with increased odds of elevation in PNES subjects. [9]

In a cross-sectional study, the diagnostic value of Multiphasic Personality Inventory Minnesota 2 (MMPI-2) was assessed in 209 patients with either PNES, PNES combined with seizures, or patients with seizures only; the reference was video-EEG. In a clinical scales model (comprising sex, hypochondriasis and paranoia), sensitivity and specificity were 77.1% and 76.8% respectively, with a percentage of correct classification of 76.8%.

In a content scales model comprising sex, HEA (health concerns) and FRS (fears), sensitivity and specificity were 65.7% and 78.0% respectively, with a percentage of correct classification of 75.9%. No significant differences were found between models. The authors concluded that "MMPI-2 had moderate validity for the diagnosis of PNES in patients referred to an epilepsy unit", however utilisation of content scales did not significantly enhance clinical scales results. [10]

A cohort study assessed a self-reported symptom questionnaire in 386 patients with diagnosed epilepsy, 308 patients with diagnosed PNES, and 371 patients with diagnosed syncope. The analysis concentrated on transient loss of consciousness (TLOC). PNES patients had a significantly higher number and frequency of TLOC related symptoms compared with epilepsy or syncope patients (p <0.001) and pairwise logistic regression analysis correctly classified 91% of patients with epilepsy versus those with syncope, 94% of those with PNES versus those with syncope, and 77% of those with epilepsy versus those with PNES. Comparable findings were found following multinomial logistic regression analysis. [11]

Other differential diagnostic studies

A study in 1365 patients with ES only, possible PNES only, mixed PNES and ES, PSLE or inconclusive monitoring evaluated comorbid diagnoses and medication history for differential diagnosis of PNES and ES. A multivariate logistic regression model differentiated PNES only from ES only with a prospective accuracy of 78% and area under the curve of 79%. Medication and number of co-morbidities were greater predictors of seizure type compared with a particular comorbidity. However, certain co-morbidities were significantly associated with PNES (asthma, chronic pain, migraines p<0.01) and ES (diabetes and non-metastatic neoplasm, p<0.01). [12]

A total of 201 children with history of one or more episodes of loss of consciousness and diagnosed as having neurally mediated syncope or epilepsy were enrolled in a prospective study to determine the use of Calgary and modified Calgary score in differential diagnosis. There were significant differences in median Calgary score between syncope [-4.00 (-6, 1)] and epilepsy [2 (-3, 5)] (z = -11.63, P < 0.01) and in median modified Calgary score between syncope [-4.00 (-6, 1)] and epilepsy [3 (-3, 6)] (z = -11.71, P < 0.01). Scores greater than or equal to 1 produced high sensitivity and specificity for both Calgary score (91.46 and 95.80% respectively) and modified Calgary scores (92.68 and 96.64% respectively), both indicating a diagnosis of epilepsy. The sensitivity and specificity of modified Calgary score and Calgary score did not show significant differences (P > 0.05). [13]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts advised that the recommendation needed updating due to new International League Against Epilepsy (ILAE) guidelines on diagnosis and classification of epilepsy and ILAE Official Report: A practical clinical definition of epilepsy. These reports consider that epilepsy may be diagnosed after single seizure if there is a high risk of further seizures occurring; additional discussion may
be required as to when an individual may be considered not to have epilepsy.

One topic expert also suggested that there is an inadequate focus on non-epileptic seizures, and noted these patients can make up to one-third of patients referred to secondary care with refractory epilepsy. However, non-epileptic seizures are outside the scope for this guideline.

Impact statement

There is mixed evidence concerning the sensitivity and specificity of screening, review of system and personality questionnaires, clinical decision rules and investigations of comorbidity in diagnosing epilepsy and differentiating between different types of seizures.

The changes in agreed ILAE criteria for diagnosing epilepsy should be considered in the update of the guideline.

New evidence identified that may change current recommendations.

1.6 Investigations

Recommendations in this section of the guideline

1.6.1 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]

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

Electroencephalogram (EEG)

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

1.6.4 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]

1.6.5 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]

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

1.6.7 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]

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

1.6.9 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]

1.6.10 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]

1.6.11 For children, young people and adults in whom epilepsy is suspected, but who present diagnostic difficulties, specialist investigations should be available. [2004]
1.6.12 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]

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

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

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

1.6.16 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]

1.6.17 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]

1.6.18 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]

**Neuroimaging**

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

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

1.6.21 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]

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

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

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

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

**Other tests**

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

1.6.27 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]

1.6.28 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]
1.6.29 A 12-lead ECG should be performed in adults with suspected epilepsy. [2004]

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

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

Neuropsychological assessment

1.6.32 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]

1.6.33 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]

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

** 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.

2018 surveillance summary

Electroencephalogram (EEG)

Duration of EEG

A retrospective study assessed the effect of limiting duration of continuous video EEG in an epilepsy monitoring unit on the diagnostic yield. Data from 2 epilepsy monitoring units were analysed (n=560), one of which is open only from Monday to Friday, limiting the duration of observation to 5 days. The event capture rates were 74% for the institution without time limits and 72% for the institution with the 5-day time limit (statistical analysis of the outcome was not reported in the abstract). The time until first event was significantly longer in the institution with the 5-day time limit than in the institution without a time limit; however, this was less than 5 days at both institutions; however the abstract did not report the p-value for this outcome. [14]

A study assessed a time varying approach for constructing functional connectivity networks from EEG data for diagnosis of epilepsy in children. Eleven children with epilepsy and 7 control children were studied. Functional connectivity networks were significantly different between children with epilepsy and controls. The system was able to diagnose paediatric epilepsy with accuracy of 89%, sensitivity of 82% and specificity of 100%. [15]

Specialist interpretation of EEG

A study assessed the intra-rater and inter-rater reliability of EEG interpretation. During two distinct time intervals, 6 clinical neurophysiologists classified EEGs into one or more of 7 diagnostic categories and assigned a subjective confidence to their interpretations. Each EEG was read by 3 people, each reader interpreted 150 unique studies, and 50 studies were re-interpreted to generate intra-rater data. The contribution of the EEGs, readers, and the interaction between the EEGs and readers to interpretation variance were analysed. Five of the six readers had a median confidence of 99% or higher. Intra-rater agreement ranged from 0.33 to 0.73 with an aggregated value of 0.59. Inter-rater agreement ranged from 0.29 to 0.62, with an
aggregate value of 0.44. Variance due to the EEGs was 65.3%, due to readers was 3.9%, and due to the interaction between readers and EEGs was 30.8%. [16]

**Automatic and computer-aided EEG interpretation**

A study assessed a supervised machine learning approach to classify seizure and non-seizure records using an open dataset (n=342). The machine learning approach improved on existing studies by up to 10%, with sensitivity of 93%, specificity of 94%, and an area under the curve of 98%. However, the abstract did not describe the 'existing studies' used as the comparator. [17]

A study assessed quantitative EEG spectrogram (Persyst 12 EEG software) in distinguishing epileptic from non-epileptic events in people with paroxysmal non-epileptic events (n=17), captured during EEG monitoring compared with a control group of patients with epileptic seizures of similar semiology (n=13). Assessment of raw EEG was the gold standard against which epileptic and non-epileptic events were validated. Quantitative EEG spectrograms were interpreted as indicating a seizure if it showed a visually significant change from baseline at the time of the clinically identified event. Eighty-two clinically identified paroxysmal events were analysed (46 non-epileptic and 36 epileptic). The quantitative EEG spectrogram correctly classified 71% of non-epileptic events and 81% of epileptic seizures. Additionally, rhythmicity spectrogram correctly classified 61% of non-epileptic events and 75% epileptic events. Fast Fourier transform spectrogram correctly classified 65% of non-epileptic events and 69% epileptic events. Asymmetry relative spectrogram correctly classified 48% of non-epileptic events and 69% epileptic events; and integrated-amplitude EEG spectrogram correctly classified 59% of non-epileptic events and 75% epileptic events. [18]

A study assessed the use of compressed spectral array EEG data in assisting expert review of continuous EEG in patients admitted to hospital (total 2,092 hours of EEG recording). Three neurophysiologists reviewed the reported findings of the first 30 minutes of 118 continuous EEGs, then used CSA to guide subsequent review. Reviewers viewed 120 seconds of raw EEG data surrounding suspicious CSA segments. The same neurophysiologists performed independent page-by-page conventional visual interpretation all continuous EEGs. Independent conventional review by 2 additional, more experienced neurophysiologists was the gold standard. Reviewing 24 hours of EEG data was significantly faster for compressed spectral array EEG data than for conventional EEG data. Longer review was necessary for both compressed spectral array EEG data and conventional EEG data when seizures were detected, but the compressed review remained faster than conventional review. Compressed spectral array-guided review was sensitive for seizures (87.3%), periodic epileptiform discharges (100%), rhythmic delta activity (97.1%), focal slowing (98.7%), generalised slowing (100%), and epileptiform discharges (88.9%). [19]

**Sleep or sleep-deprived EEGs**

A retrospective study assessed the value of EEG containing sleep compared with an EEG of awake time only in children aged 6 months to 16 years (n=425 recordings). Recordings with less than 10 minutes of awake time or at least 5 minutes of sleep were excluded. Additional yield of sleep was considered if at least one of the following was observed: appearance of interictal epileptiform activity or increase by more than 50%; or interictal epileptiform activity change in localization or morphology, seizure occurrence. Overall, 194 recordings (45.6%) showed an additional yield during sleep, which was significantly higher when interictal epileptiform activity was detected during wakefulness. The yield was significantly lower in recordings performed for non-epileptic referrals. [20]
A retrospective cohort study examined whether ambulatory EEG (aEEG) has similar diagnostic accuracy as sleep deprived EEG (sdEEG) and identified 104 patients with an unprovoked first seizure and a normal routine EEG which was followed by either an ambulatory EEG (aEEG) or sleep deprived EEG (sdEEG). Patients were followed for 1 year. Sensitivities for sdEEG and aEEG were 45% (specificity 91%) and 63% (specificity 95%), respectively. Interictal epileptiform discharges on the subsequent EEG’s were found an independent risk factor for seizure recurrence within a year (Relative risk of 1.5). The authors concluded that sdEEG and aEEG have similar diagnostic accuracies. [21]

A retrospective study assessed sleep-deprived EEG compared with standard EEG in people with suspected epilepsy (n=237). All participants underwent both EEG methods, and 69 participants had a final diagnosis of epilepsy. Seventeen of the patients with epilepsy showed interictal epileptiform patterns in EEGs after sleep deprivation (sensitivity of 25%). Sensitivity of EEG after sleep deprivation was higher in patients with primary generalised epilepsies compared with patients with focal epilepsies. However, EEG after sleep deprivation was not more sensitive than a subsequent repeated standard EEG, which was done in a subgroup of 55 patients. [22]

Use of video EEG
A study assessed standard compared with long-term video EEG in patients older than 65 years with suspected non-convulsive seizures (n=43). All participants underwent long-term video EEG (time period not defined in the abstract), and the first 20 minutes of each was used at the standard EEG. Epileptiform discharges were detected on standard EEG in significantly fewer people than on long-term EEG. Non-convulsive seizures were recorded in 1 person by standard EEG and in 4 people on long-term EEG. The median time to occurrence of the first epileptiform activities was 46.5 minutes. Epileptiform activity occurred during sleep in 33% patients with a negative standard EEG. [23]

A retrospective study used video-EEG analysis to compare ictal phase duration and the diagnostic utility of ictal duration in distinguishing between both seizure groups in 138 patients with either psychogenic non-epileptic seizures (PNES) or epileptic seizures (ES). Mean ictal phase duration was significantly greater in PNES (148.7s, 95% CI: 115.2-191.8) compared with ES patients (47.7s, 95% CI: 37.6-60.6), with higher odds (odds ratio: 23.8, 95% CI: 7.9-71.3) of being PNES (24 times higher) when ictal phase was greater than or equal to 5 minutes. Receiver operating characteristics (ROC) curves examined the diagnostic accuracy of ictal duration in distinguishing between seizure groups producing an area under the curve of 0.80 (95% CI 0.73-0.88). A cut off value of 123.5 seconds was identified as the "optimal threshold" in diagnosing PNES, with sensitivity and specificity of 65% and 93% respectively. [24]

A retrospective study with patients (n=64) with either localization-related epilepsy (LRE) and genetic generalised epilepsy (GGE) and non-epileptic attacks (NEAs) were examined on the occurrence of index-finger pointing (IFP) during generalised convulsions by video-EEG analysis to aid in epilepsy classification. The investigators found that IFP significantly occurred more in generalised tonic-clonic seizures in epilepsy patients than in convulsive NEAs (83.6% versus 12.0%; p<0.001) and was also significantly more frequent in LRE compared to GGE patients (96% versus 56.6%; p<0.001). There were no differences between the occurrence of IFP ipsilateral, contralateral, bilateral in LRE or GGE subjects and the mean angle of IFP at the metacarpophalangeal joint was found to be 35.8 degree (SD 22.0 degree) and 3.0 degree (SD 7.2 degree) in "pointers" and "nonpointers" respectively. [25]
epileptic attacks (NEA) were assessed on the occurrence of hand postures during generalised convulsions by video-EEG analysis to aid in differential diagnosis and epilepsy classification. The investigators found that LRE patients mostly demonstrated index-finger pointing (96%), GGE patients mostly demonstrated fanning at onset (91.3%) and NEA patients displayed flaccid hand posture (56%). Epileptic seizures significantly more often displayed fisting, fanning and index-finger pointing hand postures compared with NEA (74.0% versus 32.0%, p = 0.0003; 60.3% versus 20.0%, p = 0.0005; 83.6% versus 12.0%, p < 0.0001). NEA significantly more often displayed flaccid posture compared with epileptic seizures (56.0% versus 15.1%, p = 0.0001) and NEA patients were the only subgroup to display claw hand posture during NEA. [26]

A study assessed 24-hour video EEG compared with routine EEG for detecting epilepsy in children (number of participants not reported in the abstract). Clinical diagnosis of epilepsy with a minimum of 1 year of follow-up was the gold standard. When the video EEG did not capture any events, the sensitivity was 54% and specificity was 88%. The sensitivity of video EEG was higher than that of routine EEG (values not reported in the abstract), but specificity was similar. [27]

A retrospective study assessed the use of prolonged video EEG in people with suspected epileptic seizures (n=446) compared with suspected psychogenic non-epileptic seizures (n=150). Receiver operating characteristic (ROC) curves to determine optimal cut off points for length of stay based on futility were calculated. People admitted for suspected psychogenic non-epileptic seizure were significantly more likely to have an inconclusive admission. There was no significant difference in the likelihood of having an inconclusive admission if monitoring was continued for any duration in patients with epileptic seizures (area under curve [AUC] 0.46). For patients with psychogenic non-epileptic seizures, stay of 5 days or more was associated with an increased risk of the stay being inconclusive. Although the optimum cut off was 5.5 days, it did not predict outcomes well (AUC 0.52, sensitivity 0.55, specificity 0.5). [28]

A study assessed routine EEG (n=335) compared with 3-hour outpatient video EEG (n=281) and 48-hour inpatient video EEG (n=247). The 3-hour outpatient video EEG recorded significantly more seizure events than routine EEG, and the 48-hour inpatient video EEG had a significantly higher diagnostic yield than the 3-hour outpatient EEG. The time to the first epileptiform discharge was shorter for patients with generalised epilepsy than for those with localised epilepsy. [29]

A retrospective analysis assessed the yield of non-elective video EEG compared with elective video EEG in adults aged 18 to 92 years (n=304). The diagnostic yield was similar – 66% for non-elective video EEG and 69% for elective video EEG; however the abstract did not report statistical analysis of this result. Non-elective video EEG included significantly fewer patients with known epilepsy, the session duration was significantly shorter, and seizures and interictal epileptiform discharges were recorded less frequently compared with elective video EEG. [30]

A study assessed the utility of dynamic compared with conventional video EEG in children with epilepsy (n=200). The authors did not define how dynamic video EEG differed from conventional video EEG. There were no significant differences in the course of disease, seizure frequency and age between the two groups. The detection rate of epileptiform discharges was significantly higher with dynamic video EEG than with conventional video EEG. The accuracy and specificity of monitoring in the V-EEG were significantly higher than in the routine monitoring group (P<0.01). Seizure frequency and number of epilepsy attacks in patients in the V-EEG group were significantly lower than in the routine monitoring group (P<0.01). [31]
Variations of EEG

A study assessed conventional EEG administered by a registered technician compared with StatNet electrode EEG administered by a 'trained epilepsy fellow' for identification of non-convulsive status epilepticus (n=17). Each patient received both methods of EEG. The inter-observer agreement for detection of abnormal findings was 0.83 for StatNet and 0.75 for conventional EEG. The StatNet EEG took less time to arrive and to set up than conventional EEG. There was no significant difference in the 'percentage of artifact duration' between the EEG methods. [32]

A study assessed prolonged ambulatory EEG in people who had undergone a routine EEG immediately before the ambulatory EEG (n=72). The median duration of ambulatory EEG was 22.5 hours. The sensitivity of ambulatory EEG was more than double that of routine EEG when a positive test was defined as epileptiform discharges. However, the sensitivity between the two types of EEG was not significantly different if a positive test was defined included non-epileptiform abnormalities. The tests showed no significant differences in specificity. Epileptic seizures were recorded in 26% of the ambulatory EEGs, but in 0 of the routine EEGs. [33]

A retrospective study assessed a reduced electrode array (7 electrodes) compared with the standard array of 10–20 electrodes. Overall, clips from 100 recordings (50 ictal and 50 non-ictal) were selected and the electrodes were reduced digitally before blind review by 2 specialists. For the detection of any seizure, the reduced array EEG had a sensitivity of 70% and specificity of 96%. Sensitivity for identifying encephalopathic patterns was 62% and specificity was 86%. Focal seizures were more readily identified by the reduced array than were generalised ictal patterns. The authors concluded that the reduced electrode array was insufficiently sensitive for seizure detection. [34]

A study assessed interictal EEG in children diagnosed with partial epilepsies (n=35) compared with children in whom the diagnosis of epilepsy was excluded (n=35). The authors aimed to develop a multivariable diagnostic prediction model based on EEG functional network findings. Periods of resting-state EEG, free of abnormal slowing or epileptiform activity, were selected to construct functional networks of correlated activity. Multiple network characteristics previously used in functional network epilepsy studies were calculated used to build a decision tree based, prediction model. Based on epileptiform EEG activity only, EEG results supported the diagnosis of epilepsy with a sensitivity of 77% and specificity of 91%. The prediction model had a sensitivity of 96% and specificity of 95% in correctly differentiating patients from controls (AUC 89%). [35]

A study assessed the yield of 24–72 hour ambulatory EEG in people aged 60 years and older (n=156). Potentially diagnostic findings were seen in 37% of patients, which were classed as epileptiform discharges, an epileptic seizure, or a typical non-epileptic event. Focal slowing on routine EEG predicted epileptiform abnormalities on ambulatory EEG. Longer duration of ambulatory EEG was associated with increased likelihood of capturing a typical non-epileptic event. Age, the presence of a focal lesion on MRI, and duration of ambulatory EEG did not predict epileptiform abnormalities on ambulatory EEG. [36]

A UK-based safety study assessed photic stimulation during EEG in adults and children (n=5,383). Photic stimulation elicited generalised photoparoxysmal responses in 79 patients (1.5%) who had no generalised epileptiform discharges during standard EEG. Seizures were provoked in 39 patients (0.7%), including 2 generalised tonic-clonic seizures. Non-epileptic attacks were provoked in 49 patients (0.9%). Photic stimulation yielded potentially useful information in 3.1% of patients, and in 2.3%, photic stimulation
provided the only useful information in the EEG. [37]

A study assessed the effects of hyperventilation as an EEG activation method in 22 patients with focal epilepsy and 22 control participants. Standard low-resolution electromagnetic tomography was used to analyse the neural generators of the EEG signal and computed EEG lagged coherence, an index of functional connectivity, between 19 regions of interest, and built a weighted graph for each band in every subject, and characteristic path length and clustering coefficients were calculated. Hyperventilation significantly increased EEG neural generators; particularly in the cingulate cortex. Functional connectivity was increased by hyperventilation in delta, theta, alpha, and beta bands in the epileptic group but only in theta band in the control group. Intergroup analysis of mean lagged coherence, clustering coefficients and characteristic path length showed significant differences for group, condition and band. Analysis of variance for characteristic path length also showed significant interactions for group x condition and group x band. [38]

EEG in the emergency department

A retrospective study assessed EEG in the emergency department after a first seizure in patients aged 17 years or older who were candidates for discharge without anti-epileptic drug treatment (n=71). Patients who had laboratory tests or neuroimaging that appeared to identify the cause of the seizure were excluded. A 30-minute EEG was performed in the emergency department by an EEG technician. EEGs were read by a second, blinded specialist. Overall, 24% of the patients had a diagnosis of epilepsy. Inter-rater agreement for EEG interpretation was 69%. [39]

A prospective study assessed clinical and EEG findings in people admitted to an emergency department with seizure or seizure-like symptoms (n=110). EEG was advised for all patients after an initial evaluation. Before EEG, the emergency department physician and neurologist were asked clinical questions about the patient. The sensitivity and specificity of ED physicians’ diagnosis of the presence of seizure were both 88%. The inter-observer reliability for emergency department physicians and neurologists was reported to be moderate. Patients with abnormal EEG results were prescribed new medication and changes in therapy significantly more often than for patients with normal results. [40]

Salzburg criteria

A retrospective study assessed the diagnostic accuracy of the EEG criteria for diagnosis of non-convulsive status epilepticus proposed by a panel of experts at the fourth London-Innsbruck Colloquium on Status Epilepticus in Salzburg in 2013 (Salzburg criteria). EEG recordings from patients admitted for neurological symptoms or signs to three centres in Denmark and Austria. Participants aged 4 months and older were included from the centres in Denmark, and were older than 18 years in the Austrian centre. Participants were sorted into two groups: consecutive patients under clinical suspicion of having non-convulsive status epilepticus (the clinical validation group, n=120) or consecutive patients with abnormal EEG findings but no clinical suspicion of non-convulsive status epilepticus (the control group, n=100). Two raters blinded to all other patient data retrospectively analysed the EEG recordings and, using the Salzburg criteria, categorised patients as in non-convulsive status epilepticus or not in non-convulsive status epilepticus. The reference standard was inferred from all clinical and para-clinical data, therapeutic response, and the final outcome. According to the reference standard, 36% of patients in the validation group had non-convulsive status epilepticus. In the validation cohort, sensitivity of the Salzburg criteria was 97.7%, specificity was 89.6%, and overall accuracy was 92.5%. Positive predictive value was 84.0% and negative predictive value was 98.6%. Three people in the control group fulfilled the
Salzburg criteria and were therefore false positives (specificity 97.0%, sensitivity not calculable). Inter-rater agreement was high for both the Salzburg criteria (87%) and for the reference standard (95%). Therapeutic changes occurred significantly more often in the group of patients fulfilling Salzburg criteria than in those who did not. [41]

A retrospective study assessed the Salzburg Criteria for diagnosis of non-convulsive status epilepticus. EEGs of 50 non-hypoxic patients with diagnosis of non-convulsive status epilepticus at discharge and 50 controls with abnormal EEGs. In patients without pre-existing epileptic encephalopathy, the following criteria were applied: more than 25 epileptiform discharges per 10-second epoch (that is more than 2.5 per second) and patients with epileptiform discharges less than or equal to 2.5 per second or rhythmic delta/theta activity exceeding 0.5/s and at least one additional criteria. The additional criteria were clinical and EEG improvements from antiepileptic drugs, subtle clinical phenomena, or typical spatiotemporal evolution. In cases of fluctuation without evolution or EEG improvement without clinical improvement, possible non-convulsive status epilepticus was diagnosed. For identification of rhythmic delta/theta activity, the following criteria were compared: (test condition A) continuous delta-theta activity without further rules, (B) American Clinical Neurophysiology Society's (ACNS) standardised critical care EEG terminology criterion for rhythmic delta activity, and (C) ACNS criteria for rhythmic delta activity and fluctuation. False positive rates in controls dropped significantly from 28% (condition A) to 2% (condition B) and to 0% (condition C). Application of test condition C in the group with non-convulsive status epilepticus gave one false negative (2%). Possible non-convulsive status epilepticus was diagnosed based on fluctuations in 57.1% and EEG improvement without clinical improvement in 14.2%. [42]

**Neuroimaging**

An observational study assessed early comprehensive care compared with standard care in people presenting to the emergency department with a first unprovoked seizure (n=183). Standard care (n=70) involved consultation in the emergency department, EEG and CT. Early comprehensive care (n=113) involved an epilepsy specialist consultation in the emergency department, routine or long-term EEG, MRI, and 3 follow-up consultations. Long-term EEG and MRI investigations were performed significantly more often in people in the early comprehensive care group. A final diagnosis was obtained in significantly more people in the early comprehensive care group than in the standard care group. Significantly more people in the early comprehensive care group attended a 3-month follow-up appointment than in the standard care group. At 12 month follow-up, the time to first recurrence was significantly longer in the early comprehensive care group. [43]

**MRI strength**

A study assessed MRI of differing strengths (1.5 tesla and 3 tesla) in patients who received MRI of both strengths (n=804). Scans at 1.5 tesla were conducted in 1995–2004 and scans at 3 tesla were conducted in 2004–2011. Most participants had focal epilepsy. On the second scan, 37% were normal and 20% showed incidental findings. Positive findings included hippocampal sclerosis (13%), malformations of cortical development (8%), other abnormalities (4%) and previous surgery (18%). A total of 37 (5%) relevant new diagnoses were made on the 3T scans not previously seen at 1.5T. [44]

**PET-MRI versus PET-CT**

A study assessed PET-MRI compared with PET-CT for identifying the focus of seizures in children aged 2–19 years with localised epilepsy (n=35). All imaging was independently reviewed by 5 readers. The image quality did not differ significantly between the two methods. The accuracy of PET-MRI was not
inferior to that of PET-CT for localisation of a seizure focus. [45]

EEG versus MRI
A retrospective diagnostic study assessed EEG and MRI in children aged 1 month to 18 years who had a first non-febrile seizure (n=248, 63% generalised, 36% focal). EEG results were pathological in 35% of participants, and MRI showed probable epileptogenic lesions in 23%. In the following 48 months, almost a third of children had further seizures, which were significantly related to EEG findings. EEG had sensitivity of 60%, specificity of 78% and positive predictive value of 52%. MRI had sensitivity of 36%, specificity of 74% and positive predictive value of 34%. [46]

Other tests
Biomarkers
A retrospective case-control study assessed markers to predict diagnosis of occipital lobe epilepsy (OLE). 19 patients with OLE and 57 with temporal lobe epilepsy (TLE) were identified; three sequential case-control patients with TLE were matched with each patient with OLE. Visual symptoms occurred in patients with OLE (8/19) but not patients with TLE (P < 0.0001). Occipital interictal spikes (IIS) occurred in only 6 patients with OLE (P < 0.0001). IIS in the posterior temporal lobe occurred in five with OLE and one with TLE (P = 0.003). IIS involved more than one lobe of the brain occurred in 11 patients with OLE (11/19) and 9 with TLE group. (P = 0.0003) Multilobar resection was needed in 15 patients with OLE but in only one with TLE (P < 0.0001). [47]

A prospective cohort study with epilepsy patients (n=78) examined whether postictal transient hyperammonemia can distinguish between different seizure types. Patients were classified according to seizure type: generalised convulsive seizures (GCS), psychogenic nonepileptic seizures with convulsions (PNES-C), or focal seizures (FS). In an epilepsy monitoring unit, ammonia levels were checked at baseline, within 1 hour of the event and in some patients 24 hours after the event. The investigators reported that ‘the change in ammonia postictally from baseline was significantly different among the three groups (p=0.004). The area under the receiver operator characteristic (ROC) curve for postictal ammonia to distinguish GCS from other groups was 0.88 (95% confidence interval [CI] 0.69-0.96) suggesting ammonia be a good test for differentiating epileptic GCS from other events An ammonia level of >80 mumol/L correctly classified 80% of our patients (sensitivity 53.9%, specificity 100%). [48]

A cross-sectional study undertook venous blood gas analysis in individuals (n=94) who visited the emergency department after seizure episodes. Venous blood gas analysis 1-hour post seizure found values of: pH<7.245 [sensitivity 80% (95% CI: 44-96), negative predictive value 96.9% (95%CI: 88.3-99.4)], bicarbonate<17.1 mmol/L [sensitivity 80% (95%CI: 44-96), negative predictive value 97% (95%CI: 89-99.5)], base excess<-11.1 mEq/L [sensitivity 80% (95%CI: 44-96), negative predictive value 97% (95%CI: 89-99)], and lactate>7.65 mmol/L [sensitivity 80% (95%CI: 44-96), negative predictive value 96.6% (95%CI: 87-99)]. The investigators concluded that venous blood gas analysis for pH, base excess, lactate and bicarbonate immediately one hour after the last epileptic seizure episode, could be used to predict whether the patient will have a seizure recurrence in the emergency department. [49]

A retrospective cohort study with individuals with generalised tonic-clonic seizures (n=195) and patients with other seizures (n=106) including syncopes (n=52) psychogenic nonepileptic seizures (n=17) and complex focal seizures (n=37) assessed the value of serum lactate as a diagnostic biomarker of ‘transient loss of consciousness’. Blood samples were taken within 2 hours of the event and serum lactate levels were significantly higher in
patients with generalised tonic-clonic seizures p<0.001) compared to other seizure types. The area under the receiver operator characteristic (ROC) curve was 0.94 (95% CI 0.91-0.96). For a cut-off concentration of 2.45mmol/l, the sensitivity was 0.88 and the specificity 0.87. [50]

A prospective cohort study with individuals (n=85) presenting at emergency department, with generalised tonic-clonic seizures (GTCS) or syncope assessed serum concentrations of creatine kinase (CK) and lactate as biomarkers to distinguish between different epilepsies. Serum lactate levels were significantly greater in GTCS patients compared to syncope patients whilst there were no differences between patient groups with CK. Serum lactate was highly sensitive and specific at a cut off of 2.45mmol/l at 1 hour post event in distinguishing GTCS as a causal factor for "impairment of consciousness" from syncope with high sensitivity (0.94) and specificity (0.93), comparable results were found for second hour post seizure. [51]

Ictal-interictal continuum (IIC) continuous EEG (cEEG) patterns are associated with poor outcomes in epilepsy and may represent "electroclinical" status epilepticus. In a cross sectional study with hospitalised individuals (n=18) FDG-PET imaging was evaluated as a complementary metabolic biomarker of status epilepticus among patients with IIC cEEG patterns. FDG-PET hypermetabolism was common (61%) and significantly predicted electrographic and electroclinical status epilepticus; sensitivity 79% [95% CI 53-93%], and specificity 100% [95% CI 51-100 %] p=0.01. [52]

Patients attending emergency department due to seizures (n=40) or control subjects (n=40) were assessed on arrival and four hours later to determine levels of ischemia-modified albumin/albumin ratios in study and control groups were 1555.3 IU/g and 462.4 IU/g (P < .001) initially and 1431.4 IU/g and 383.6 IU/g (P < .001) at follow up, respectively. [53]

The use of serum metalloproteinase-3 (MMP-3) levels as a biomarker for diagnosis of epilepsy was assessed in 227 individuals with epilepsy and 97 healthy control individuals. Individuals with epilepsy had significantly lower serum MMP-3 levels than those in the control group. Levels of serum MMP-3 were significantly greater in males compared to females, and in both epilepsy and control subjects, were strongly correlated with age. For age 20-40 years, cut-off values for MMP-3 in 23.87ng/ml and 12.31ng/ml in males and females respectively, the sensitivity and specificity for patients with epilepsy versus controls were 72.22% and 76.67% for males, and 45% and 94.12% for females. For age >=40 years with cut-off MMP-3 concentrations of 20.70ng/ml and 10.92ng/ml, sensitivity and specificity were 85.71% and 47.62% versus 85.62% and 100% for male and female groups, respectively. The investigators concluded that MMP-3 as a diagnostic tool in epilepsy is dependent on sex of patients and is limited to certain age brackets. [54]

A study assessed the utility of serum metalloproteinase-2 (MMP-2) levels as a biomarker for diagnosis of epilepsy in 233 individuals diagnosed with epilepsy or 97 health control subjects. Individuals with epilepsy had significantly lower serum MMP-2 concentrations compared with control subjects. In both subjects with epilepsy and control subjects, age was significantly correlated with serum MMP-2 levels and no significant gender differences were observed. A concentration cut off value of 175.40ng/ml produced a sensitivity of 71.13% and a specificity of 62.66% in differentiating epilepsy subjects from control. [55]

A retrospective study with individuals (n=270) diagnosed with either generalised tonic-clonic
seizures (GTCS), psychogenic nonepileptic seizures (PNES) or syncope, assessed serum lactate as a diagnostic biomarker for distinguishing between different epilepsy events. Serum lactate levels were significantly increased in GTCS patients compared with PNES and syncope patients. Serum lactate levels in female GTCS patients were significantly greater than in males, however the suggested cut-off value of 2.43 mmol/l whilst providing a high specificity for both gender groups produced a sensitivity of 0.85 and 0.64 for males and females respectively, therefore such cut-off point "might not have a discriminative effect between GTCS, PNES, and syncope in female patients". [56]

A study assessed 90 patients with epilepsy and control subjects (unclear on total number of subjects in each arm) to determine expression of four epilepsy-associated microRNAs (miR-106b, miR-146a, miR-194-5p and miR-301a) by serum analysis. Three microRNAs (miR-106b, miR-146a and miR-301a) were significantly increased; miR-194-5p was significantly lowered in epilepsy subjects compared with control. Both miR-106b and miR-146a were correlated with NHS3 score in epilepsy subjects and receiver operating characteristic (ROC) value for miR-106b was the highest result in predicting epilepsy (AUC=0.786) compared to serum miR-146a (AUC=0.774), miR-194 (AUC=0.686) or miR-310a (AUC=0.696). Combination of both miR-106b and miR-146a improved sensitivity/specificity for prediction of epilepsy (AUC=0.887). [57]

**Signs and symptoms of epilepsy**

A systematic review including 5 studies focusing on the presence of urinary incontinence in epileptic seizures (ES) and non-epileptic events (NEE) such as psychogenic nonepileptic events (PNEEs) and syncope, as a diagnostic aid in distinguishing between ES and NEEs. The investigators found pooled accuracy measures of urinary incontinence (ES versus NEEs) yielded sensitivity 38%, specificity 57%, positive likelihood ratio of 0.705-1.095) and negative likelihood ratio of 1.092 (95% CI 0.941-1.268). Comparing seizure groups (epileptic seizures versus NEEs; ES versus syncope; ES versus PNNEes) resulted in non-significant positive likelihood ratio for pooled accuracy measures for urinary incontinence. The authors concluded that urinary incontinence provided no benefit as a diagnostic aid in distinguishing between ES and NEEs. [58]

**Accelerometer-based diagnosis**

A study assessed accelerometer-based time-frequency mapping for differentiating between epileptic seizures and psychogenic non-epileptic seizures (n=35; 56 events). Twenty-six patients had psychogenic non-epileptic seizures, eight had epileptic seizures, and one had both seizure types. The time-frequency maps were derived from fast Fourier transformations to determine the dominant frequency for sequential blocks for the course of each event. The coefficient of variation of limb movement frequency was less for psychogenic non-epileptic seizures than for the epileptic seizure events. A blinded review of the time-frequency maps by an epilepsy specialist was accurate in differentiating between the event types, that is, 38 of 41 non-epileptic (92.7%) and 8 of 6 epileptic seizures (75%), were diagnosed correctly, with 7 events classified as non-diagnostic. Using a coefficient of variance cut-off score of 32% resulted in similar classification accuracy, with 42 of 45 non-epileptic (93%) and 10 of 11 epileptic seizure (91%) events correctly diagnosed. [59]

**Electromyography**

A study assessed electromyography using a wearable device for the automatic detection of generalised tonic-clonic seizures in people referred for long-term video-EEG monitoring on generalised tonic-clonic seizures (n=71). Seizure detection was real-time and fully automated. The reference standard was the evaluation of video-EEG recordings by trained experts, who were blinded to data from the device. Reading the seizure logs from the
device was done blinded to all other data. The mean recording time per patient was 53 hours and the total recording time was 3736 hours, and device deficiency time was 193 hours (4.9% of the total time the device was turned on). The sensitivity of the wearable device was 93.8% (30 of 32 generalised tonic-clonic seizures were detected). Median seizure detection latency was 9 seconds, and the false alarm rate was 0.67 per day. [60]

**Diagnosis after a first seizure**

A prospective observational study assessed diagnosis of idiopathic partial epilepsies after the first unprovoked focal seizure in children aged 1 month to 17 years (n=107) who were followed-up for at least 5 years. A specific syndrome (childhood epilepsy with centro-temporal spikes, Panayiotopoulos syndrome and, idiopathic childhood occipital epilepsy of Gastaut) was diagnosed in 75% of children after a first seizure, and 90% of children had a diagnosis at the end of the 5-year follow-up. In the 27 children who had no initial classification, 11 patients (41%) had no change in diagnosis, and 16 patients (59%) were diagnosed with a specific syndrome or atypical epilepsy. [61]

A retrospective study assessed the yield of diagnostic investigations in people referred to an epilepsy clinic after a first seizure (n=219). No diagnosis of epilepsy was made in 38 people (17%), with these diagnoses mainly being reflex syncope and psychogenic non-epileptic seizures. Of the remaining 181 people who presented with seizures, 71 had evidence of previous seizures. Of the 110 patients with true first seizures, 19 were provoked, most frequently by drugs or alcohol. The emergency department had sensitivity of 74% and specificity of 32% for seizure diagnosis. In the true first seizure patients, EEG demonstrated epileptiform discharges in 22 patients (21%). CT had a 16% probability of finding a potentially epileptogenic structural abnormality and MRI had 20% probability of epileptogenic findings. [62]

A prospective study assessed the effects of investigation of the cause of first seizures in people referred to a first seizure clinic (n=200) compared with a historical cohort. Most referrals to the first seizure clinic were from general practitioners and emergency departments. The mean waiting time for first assessment was significantly shorter for the first seizure clinic cohort than for the historical cohort. A diagnosis was established at first-contact in 80.5% of cases while 16.0% of patients needed a second visit. Eighty-two patients (41.0%) were diagnosed with epilepsy. An abnormal EEG was found in 93.9% of patients diagnosed with epilepsy. Sixty-three patients were started on anti-epileptic drugs. In 18% of cases, driving restrictions were initiated. The most common non-seizure diagnosis was syncope (24.0%). [63]

**Motion capture systems**

A prospective study assessed a single-camera 3D video monitoring system (using the Microsoft Kinect camera) compared with a 6-camera motion-capture system, both used over the same bed in the epilepsy monitoring unit. The correlation between the single camera system and the 6-camera system was 84.2%. Movements of interest (n=42) arising from temporal (n=19) and extra-temporal (n=23) brain regions were analysed. The movements of interest showed significant differences in extent and displacement of the movements between the temporal and extra-temporal seizure types. Movements of interest originating from the temporal region were significantly shorter, and had higher jerking levels, compared with extra-temporal regions. The 3D approach was faster in extracting body motion trajectories. [64]

**Magnetoencephalography**

A prospective study assessed the additional yield of magnetoencephalography in people who had at least 3 normal EEGs, including sleep EEG (n=52). The reference standard was diagnosis based on the medical records after at least 1 year of follow-up.
Magnetoencephalography and EEG were performed simultaneously for 1 hour. Epilepsy was diagnosed in 22 patients, and magnetoencephalography results supported this diagnosis in 9 people. The overall sensitivity of magnetoencephalography was 41%, and the additional sensitivity over EEG alone was 18%. The specificity of magnetoencephalography was 93%, with normal magnetoencephalography in 28 of 30 patients without a diagnosis of epilepsy. [65]

A study [Jin2017] assessed resting-state functional connectivity of magnetoencephalography for differentiating between mesial temporal lobe epilepsy (n=46) and healthy controls (n=46) and between right and left mesial temporal lobe epilepsy (n=23 for each subtype), with use of machine learning algorithms. The optimum model identified people with mesial temporal lobe epilepsy with sensitivity of 96% and specificity of 94%, and differentiated left from right mesial temporal lobe epilepsy with sensitivity of 96% and specificity of 94%. [66]

**Video observation-based diagnosis**

A study assessed the accuracy of neurologists’ diagnosis based on clinical history and video recordings of paroxysmal events. Overall, 47 neurologists reviewed 12 clinical histories and videos. The median diagnostic accuracy for all paroxysmal events was significantly higher for observation (75%) than for clinical history (67%). This was largely due the difference in diagnostic accuracy in the subgroup of patients with psychogenic non-epileptic seizures (83% for observation and 67% for clinical history). Higher diagnostic accuracy and increased inter-rater agreement may be seen with higher levels of training; however the abstract did not include statistical analysis for these outcomes. Physicians with higher levels of training were more confident with diagnosis based on observation. [67]

A study assessed the accuracy of seizure diagnosis by epilepsy specialists (n=8), neurologists (n=12) and intern physicians (n=20). Overall, 150 video clips from 50 patients who each had 3 seizures of the same type were reviewed. The videos included 37 series of epileptic seizures, 8 series of physiological events, and 5 series of psychogenic non-epileptic seizures. The diagnostic accuracy for epileptic seizures and non-epileptic events increased significantly from 61% to 66% after viewing all 3 seizures. Epilepsy specialists had sensitivity of 77% and specificity of 81%; neurologists had sensitivity of 66% and specificity of 70%; and intern physicians had sensitivity of 59% and specificity of 66%. A wide range of diagnostic accuracy was found across the various seizures types – 90% for generalised tonic-clonic seizures; 80% for dialeptic seizures; 76% for automotor seizures; 53% for myoclonic seizures; 48% for hypermotor seizures; 44% for gelastic or dacrystic seizures; and 43% for psychogenic non-epileptic seizures. [68]

A study assessed physicians’ ability to recognise paroxysmal neurological events based on video observations, when blind to clinical data and final diagnosis. Overall, 12 patients’ videos were used, 6 epileptic seizures, 4 psychogenic non-epileptic seizures, and 2 other non-epileptic events. If an epileptic seizure was diagnosed, the physician was asked to classify the type of epilepsy. Participating physicians (n=145) included neurologists (59%), neuropsychiatrists (26%), neurology residents (10%), and psychiatrists (5%), most of whom (61%) were not EEG readers. The median proportion of correct diagnoses was 75%. Higher frequency of exposure to psychogenic epileptic seizures was associated with better recognition of this disorder. Physicians were significantly more accurate in diagnosing epilepsy than psychogenic non-epileptic seizures. The median proportion of correct diagnoses for epilepsy classification was 50%). [69]

**Neuropsychological assessment**

No evidence was identified.
2014 surveillance summary

Two studies looked at how psychological comorbidity and other factors relating to epilepsy and its treatment affect health-related quality of life (HRQoL) in young people and adults.

A systematic review sought to identify factors that predicted HRQoL and resource use in adults with epilepsy. Age, gender and marital status were not associated with HRQoL, whereas education level and employment status affected HRQoL evidence was inconsistent. Depression, anxiety, seizure frequency were predictive of poor HRQoL. [70]

A prospective cohort study assessed how epilepsy status and psychiatric and other comorbidities affect HRQoL in young people with epilepsy. Around one-quarter (25.6%) of young people with epilepsy had any psychiatric disorder at follow-up, more than a third (39.0%) had any neurodevelopmental spectrum disorder. A psychiatric disorder was significantly associated with worse HRQoL across the majority of the quality of life scales. [71]

Topic expert feedback

There was a mix of opinion from topic experts on whether the recommendation on investigations should be updated: 2 experts thought it should be updated, while 1 though it did not need updating. One topic expert said there was more useful information from Functional MRI and PET scanning; and another topic expert highlighted that there is an increasing role for genetics in diagnosing the underlying cause of epilepsy and said that ‘there should be guidelines about who, when and with what should be tested. There is also an increasing role for immune evaluation in some circumstances – both of these have implications for management, albeit in the latter in tertiary care’. A study on Early-Life Epilepsies and the Emerging Role of Genetic Testing which concluded that ‘genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies regardless of key clinical features’ was identified.

Initial intelligence gathering identified on-going research on Finding out the genetic cause of Juvenile Myoclonic Epilepsy which aims to find the genetic cause for Juvenile Myoclonic Epilepsy by comparing the genetic code in these patients with that in people who do not have epilepsy using clues from their EEG or brainwave test that is used to help diagnose epilepsy.

Impact statement

Overall, the new evidence supports the existing recommendations. There is some evidence that indicates a role for automated algorithms, and that machine learning may help with interpretation of EEGs in the future. [16-19] There is also emerging evidence concerning the role of genetic testing in the diagnosis of epilepsy but the data are too limited at present to be considered within the guideline.

New evidence is unlikely to change guideline recommendations.

1.7 Classification

Recommendations derived from these review questions

1.7.1 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]

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

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

Classification

2018 surveillance summary

A retrospective study assessed the International League Against Epilepsy (ILAE) definition of epilepsy (one unprovoked seizure with a probability of further seizures). Patients (n=1,006) were categorised depending on whether they had one unprovoked seizure (new definition of epilepsy; n=152) or 2 or more unprovoked seizures (traditional definition of epilepsy; n=854) at the time of epilepsy diagnosis. Patients diagnosed according to the new definition showed a higher proportion of subjects with an abnormal neurological examination and with focal seizures. The two samples differed in the presence of at least one of the factors predicting seizure recurrence (focal seizures or abnormal findings in at least one among the following: neurologic examination, EEG, and neuroimaging. Long-term recurrence in patients diagnosed with the new definition was 83.6% at 10 years and 89.1% at 15 years. The probability of early remission did not differ between the two groups. [72]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback

Two topic experts said that the recommendation should be updated to reflect the new ILAE classification, changes in terminology and clarification of definitions, which would have wider implications throughout the guideline. References were provided to several publications:

Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology

Instruction manual for the ILAE 2017 operational classification of seizure types

Classification of the epilepsies: New concepts for discussion and debate—Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus

Impact statement

The new ILAE classification, changes in terminology and definitions should be considered and reflected within this recommendation and throughout the guideline.
1.8 Management

Recommendations in this section of the guideline

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

1.8.2 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]

1.8.3 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]

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

2018 surveillance summary

A Cochrane review of 18 studies (RCTs, controlled or matched trials, cohort studies or other prospective studies with a control group, and time series studies; n=NR) evaluating the effects of any specialised or dedicated intervention beyond usual care in adults with epilepsy, identified 16 separate interventions, which were classified into 7 groups. It was noted that the specialist epilepsy nurse and self-management education had some evidence of benefit, but that most of the studies had methodological weaknesses and no single model of service provision could be recommended. [73]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The evidence supports the current recommendation concerning the use of epilepsy nurses and self-management education in the management of epilepsy.

New evidence is unlikely to change guideline recommendations.
1.9 Pharmacological treatment

Recommendations in this section of the guideline

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

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 1.9.1.10, 1.9.17.3, 1.9.17.6, 1.9.17.9 and 1.15.1.4 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).

The GDG is also aware of specific issues with prescribing sodium valproate to girls and women of childbearing age. In January 2015, the MHRA issued a strengthened warning stating that valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. Recommendations in this section offer alternative prescribing options for this group. Recommendations 1.9.1.10, 1.9.17.3, 1.9.17.6, 1.9.17.9 and 1.15.1.4 also provide additional specific information of relevance when considering prescribing AEDs to women of childbearing age.

1.9.1 General information about pharmacological treatment

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

1.9.1.2 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 E). [2004]

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

1.9.1.4 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, adult and their family and/or carers as appropriate, considers that this is not a concern. 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) 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]

1.9.1.5 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]

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

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

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

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

1.9.1.10 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]

* 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.

** Recommendations 1.1.1, 1.2.2, 1.3.3, 1.3.5 and 1.3.10 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.

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**General information about pharmacological treatment**

**2018 surveillance summary**

A Cochrane review of 6 RCTs/quasi-RCTs (2,439 participants) assessed the probability of seizure recurrence, seizure remission, mortality, and adverse effects of AEDs given immediately after first seizure unprovoked epileptic compared with controls, in children and adults. An individual participant meta-analysis was undertaken on data from 2 studies. Results indicate that immediate treatment is associated with a lower probability of relapse at one year and at five years and a higher probability of an immediate five-year remission (high quality evidence); but no difference between immediate treatment and control in terms of five year remission at any time. Antiepileptic drugs did not affect overall mortality after a first seizure. Treatment of the first seizure was associated with a significantly higher risk of adverse events compared with deferred treatment (moderate quality evidence). [74]

A Cochrane review of 10 RCTs (296 participants) evaluating the efficacy of immediate-release carbamazepine (IR CBZ) versus controlled-release carbamazepine (CR CBZ) in patients diagnosed with epilepsy concluded that ‘at present, data from trials do not confirm or refute an advantage for CR CBZ over IR CBZ for seizure frequency or adverse events in patients with newly diagnosed epilepsy’. The trials were of small size and poor methodological quality. [75]

A Cochrane review of 6 RCTs (125 participants) evaluating the efficacy and tolerability of melatonin as add-on treatment for epilepsy found that no conclusion about
the role of melatonin in reducing seizure frequency or improving quality of life in people with epilepsy could be made as the included studies were of poor methodological quality and did not systematically evaluate seizure frequency and adverse events. [76]

A Cochrane review of 3 RCTs (246 participants) evaluating the efficacy and side effect profile of sulthiame as monotherapy in people with epilepsy reported that it was not possible make any conclusions on the efficacy and safety of sulthiame as monotherapy due to small sample size, poor methodological quality and lack of data on important outcome measures. [77]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

Work was conducted by the NICE surveillance team in December 2017 to consider new advice from the Medicines & Healthcare products Regulatory Agency (MHRA) on sodium valproate use during pregnancy: Sodium valproate is a well-established treatment for epilepsy. However, treatment during pregnancy is associated with a risk of abnormal pregnancy outcomes and the MHRA website states that sodium valproate is associated with a 10% increased risk of congenital malformations, delays in early development of children and approximately 3-fold increased risk of autistic spectrum disorder and approximately 5-fold increased risk of childhood autism compared with the general study population. The association has been recognised for many years; it appears to be dose-dependent and with increased risks when valproate is taken with other medicines.

The European Medicines Agency’s experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC) and MHRA are recommending new measures to avoid exposure of babies to valproate medicines in the womb, including:

1) Valproate should be contraindicated in pregnancy and women of childbearing potential not using effective contraception.

2) This should be supported by a ‘Pregnancy Prevention Programme’.

3) A signed ‘acknowledgement’ or ‘consent’ form should be routinely used when women are reviewed on an annual basis by a specialist.

The MHRA and manufacturers have developed a Toolkit on the risks of valproate medicines in female patients which was published in February 2016 and supports informed choices about valproate use in girls and women. This will be updated to match the proposed contraindications.

The footnote concerning the MHRA division of antiepileptic drugs into 3 categories in 2013 was updated in November 2017. The MHRA have added the advice that ‘when evaluating whether continuity of supply should be maintained for category 2 or 3 drugs, consider:

- perception by patients of differences in supply, for example differences in product presentations
- co-morbid autism, mental health issues, or learning disability.’

Initial intelligence gathering identified that the guidance Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (July 2011) TA232 has been withdrawn because GlaxoSmithKline has discontinued retigabine (Trobalt) due to limited usage.

Impact statement
The new evidence supports existing recommendations concerning an AED treatment strategy; and the evidence at present does not indicate a difference in outcomes between immediate-release versus controlled-release carbamazepine in people with epilepsy. Neither melatonin nor sulthiame are recommended for use in people with
epilepsy and the current evidence does not indicate that this would change.

An editorial change is required to remove reference to retigabine; and the footnote relating to the MHRA categorisation of antiepileptic drugs needs to be updated with the latest advice.

While recommendations for the use of sodium valproate in NICE guideline CG137 already have clear warnings to alert prescribers, it is necessary to incorporate the new information on contraindications into the guideline recommendations.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.2 Initiation of pharmacological treatment

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

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

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

1.9.2.4 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]

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

1.9.2.6 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]

1.9.2.7 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]

1.9.2.8 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]
Initiation of pharmacological treatment

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The absence of new evidence indicates no need to update this section of the guideline.

No new evidence. Recommendations are unlikely to change.

Recommendations in this section of the guideline

1.9.3 Pharmacological treatment of focal seizures

First-line treatment in children, young people and adults with newly diagnosed focal seizures

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

1.9.3.2 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 and developmental risks of sodium valproate (see recommendation 1.9.1.10)**. [new 2012]

1.9.3.3 Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 1.9.3.1 and 1.9.3.2). [new 2012]

Adjunctive treatment in children, young people and adults with refractory focal seizures

1.9.3.4 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 1.9.3.1 and 1.9.3.2) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)**. [new 2012]

1.9.3.5 If adjunctive treatment (see recommendation 1.9.3.4) 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]

* 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.

** February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

2018 surveillance summary

Focal (aka partial) seizures, newly diagnosed/monotherapy

A Cochrane review undertook an individual participant data (IPD) analysis. Data were available for 595 of 1,192 eligible participants from 4 of 12 RCTs. The analysis assessed the time to withdrawal, 6 and 12 month remission, and first seizure with carbamazepine compared to phenytoin, used as monotherapy in people with partial onset seizures (simple partial, complex partial, or secondarily generalised tonic-clonic seizures), or generalised tonic-clonic seizures, with or without other generalised seizure types. There was no statistically significant difference between carbamazepine and phenytoin for these outcomes, but the authors noted that CIs were wide and they could not exclude the possibility of important differences. There were more serious adverse events with phenytoin than carbamazepine. While there was some evidence that people with generalised seizures may be less likely to withdraw early from phenytoin than from carbamazepine, misclassification of seizure type may have impacted upon the results (the authors identified up to 48 individuals with misclassification of seizure type, 32% of whom had generalised epilepsy). The authors 'recommend caution when interpreting the results of this review, and do not recommend that our results alone should be used in choosing between carbamazepine and phenytoin'. [78]

A Cochrane review of 5 RCTs (734 participants) compared the efficacy and safety of vigabatrin versus carbamazepine monotherapy for epilepsy in children and adults. Data were insufficient to address the risk-benefit balance of vigabatrin versus carbamazepine monotherapy for epilepsy. While no differences in visual field defects and visual disturbances were noted, the authors referenced an existing systematic review of observational studies that showed a high prevalence of visual field defects with vigabatrin monotherapy. [79]

A Cochrane review undertook an IPD analysis incorporating a network meta-analysis (NMA). Data was available from 12,391 of 17,961 eligible participants from 36 of 77 RCTs. The analysis compared the time to withdrawal of allocated treatment, remission and first seizure of 10 AEDs that are currently used as monotherapy in children and adults with partial onset seizures (simple partial, complex partial or secondarily generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus). For individuals with partial onset seizures, carbamazepine and lamotrigine are suitable first-line treatments and that levetiracetam may be a suitable alternative. For individuals with generalised tonic-clonic seizures (with or without other generalised seizure types), there was high-quality evidence supporting the use of sodium valproate as the first-line treatment and that lamotrigine and levetiracetam would be suitable alternative first-line treatments. [80]

A Cochrane review of IPD (data available for 1,151 of 1,239 eligible participants from 2 of 3 RCTs) evaluated the effects of topiramate monotherapy versus carbamazepine monotherapy for epilepsy in people with partial-onset seizures or generalised onset tonic-clonic seizures. In individuals with partial-onset seizures treated with carbamazepine, 12-month remission is achieved earlier and it is less likely to be withdrawn than in patients treated with topiramate. While evidence indicated no differences between the drugs and outcomes in people with generalised-onset
tonic-clonic seizures, there were only a limited number of individuals identified with these seizures (15% of the sample). [81]

A Cochrane review of IPD available for 2,572 of 3,394 eligible participants from 9 of 13 trials evaluated the effectiveness of lamotriginie monotherapy compared to carbamazepine monotherapy in people with partial onset seizures or generalised onset tonic-clonic seizures. In individuals with partial onset seizures Lamotriginie was significantly less likely to be withdrawn than carbamazepine, but carbamazepine may be superior in terms of seizure control. The results were less clear for individuals with generalised onset seizures, who made up only 12% of cases, as the study authors were concerned that seizure type may have been misclassified in up to 50% of these participants. Methodological quality of the studies was rated as generally good. [82]

A Cochrane review of IPD from 836 of 1,455 eligible participants from 6 of 13 trials evaluated pair-wise monotherapy comparisons in people with partial onset seizures or generalised onset tonic-clonic seizures. Results indicated that that carbamazepine may be more effective than phenobarbitone in terms of seizure control and adverse events; and that for time to first seizure recurrence phenobarbitone was better for partial seizures and carbamazepine for generalised seizures. The evidence was rated as low quality. [83]

A Cochrane review of 2 RCTs/quasi RCTs (163 participants) evaluated the efficacy, effectiveness, tolerability and safety of clobazam as monotherapy in people with new-onset partial or generalised seizures. In previously untreated children, there was no benefit for clobazam compared with carbamazepine for still taking treatment (retention) at 12 months. In adolescents and adults with neurocysticercosis, there was a small benefit of clobazam compared with phenytoin for retention at six months. [84]

A Cochrane review of 2 RCTs (753 participants) evaluating the efficacy and tolerability of pregabalin monotherapy in people with epilepsy, reported on the results of 1 study that found that pregabalin had similar tolerability, but inferior efficacy to lamotrigine for newly diagnosed partial seizures. However, this study was limited in design; and the review authors stated ‘data were too limited to draw any conclusions’. [85]

A Cochrane review of IPD from 480 of 517 eligible participants in 3 RCTs compared oxcarbazepine and phenytoin monotherapy in participants with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types. There was a statistically significant advantage for oxcarbazepine over phenytoin for time to treatment withdrawal, but insufficient evidence to suggest a difference between the drugs for other outcomes. When considered by seizure type, there was no significant advantage for either drug for generalised epilepsy, however oxcarbazepine is significantly less likely to be withdrawn than phenytoin in participants with partial onset seizures, but it was not possible to determine whether oxcarbazepine is equivalent, superior or inferior to phenytoin in terms of seizure control. [86]

A Cochrane review of IPD available for 669 of 1,119 eligible participants from 5 of 11 trials investigated the time to withdrawal, remission and first seizure of phenytoin compared to valproate when used as monotherapy in people with partial onset seizures or generalised tonic-clonic seizures (with or without other generalised seizure types). There was no overall difference between the drugs for these outcomes, nor any statistical interaction between treatment and seizure type. The authors noted that ‘misclassification of seizure type may have confounded the results of this review’. [87]

A Cochrane review of IPD available for 599 eligible participants from 4 of 8 trials evaluated the effectiveness of phenobarbital [phenobarbital] monotherapy versus phenytoin monotherapy in children or adults with partial
onset seizures or generalised onset tonic-clonic seizures. There was no significant differences for seizure outcomes between the 2 AEDs, but a statistically significant clinical advantage for phenytoin in terms of treatment withdrawal (the authors hypothesised that phenobarbitone may lead to more adverse effects). Neither study was blinded and there was high statistical heterogeneity between the studies. [88]

**Refractory Focal seizures**

A Cochrane review of 2 RCTs (467 participants) investigating the efficacy and safety of losigamone when used as an add-on therapy for partial epilepsy found that losigamone reduced seizure frequency, but was associated with more treatment withdrawals when used as an add-on therapy. The authors noted that the trials were of short-term duration and uncertain quality. [89]

A Cochrane review of 11 RCTs (747 participants) evaluating the short-term effectiveness of vigabatrin versus placebo in people with drug-resistant partial epilepsy found that vigabatrin reduces seizure frequency, but is associated with side-effects, in particular fatigue or drowsiness. [90]

A Cochrane review of 3 RCTs (1,311 participants) evaluated the efficacy and tolerability of lacosamide as an add-on treatment for people with drug-resistant partial epilepsy. Compared with placebo, lacosamide was effective and well tolerated in the short term in adults. Higher doses of lacosamide were associated with more adverse effects and withdrawal of the drug compared with lower doses. Quality of the evidence was rated as moderate to high. [91]

A Cochrane review of 5 RCTs (1,799 participants) evaluating the efficacy and tolerability of eslicarbazepine acetate when used as an add-on treatment for people with drug-resistant partial epilepsy found moderate to high evidence that, compared with placebo, eslicarbazepine acetate reduces seizure frequency when used as an add-on treatment for adults with drug-resistant partial epilepsy in the short-term, but is associated with adverse effects. [92]

A Cochrane review of 4 RCTs (236 participants) evaluating the efficacy and tolerability of felbamate versus placebo when used as an add-on treatment for people with refractory partial-onset epilepsy found that due to the ‘methodological deficiencies’ in the studies there is ‘no reliable evidence to support the use of felbamate as an add-on therapy in people with refractory partial-onset epilepsy’. [93]

A Cochrane review of 11 RCTs (2,125 participants) evaluating the efficacy and tolerability of gabapentin as an add-on treatment for people with drug-resistant partial epilepsy undertook a meta-analysis on data from 6 RCTs (1,206 participants). This analysis found that gabapentin significantly reduced seizure frequency and showed increasing efficacy with increasing dose, but is associated with significantly more adverse effects compared with placebo. The studies were rated as low/unclear risk of bias and were of short duration (there was no evidence for efficacy beyond three-months). [94]

A Cochrane review of 14 RCTs (1,958 participants) evaluating the effectiveness of lamotrigine compared to placebo as an add-on treatment for people with refractory partial epilepsy reported that lamotrigine was effective in reducing seizure frequency, and was fairly well tolerated, but the trials were of relatively short duration. Note, this was an update of 2010 Cochrane review, and no new studies have been included. [95]

A Cochrane review of 11 RCTs (1,861 participants) evaluating the effectiveness of levetiracetam as an add-on treatment for people with drug-resistant focal epilepsy found that levetiracetam can significantly reduce focal seizure frequency in adults and children, and is well tolerated, although non-specific changes in behaviour may be experienced in up
to 20% of children. The studies were rated as having low risks of bias. [96]

A Cochrane review of 6 RCTs (2,009 participants) evaluating the efficacy and tolerability of pregabalin add-on treatment in drug-resistant partial epilepsy reported that it is significantly more effective than placebo at achieving a 50% or greater seizure reduction and increasing seizure freedom; doses from 150 mg/day to 600 mg/day were efficacious, with increasing effectiveness at 600 mg doses (evidence rated as low/unclear risk of bias). [97]

A Cochrane review evaluating the efficacy and tolerability of stiripentol as add-on treatment for patients with focal refractory epilepsy who are taking AEDs only identified 1 RCT (32 children). There were non-significant reductions in seizure frequency and improvement in seizure freedom when add-on stiripentol was compared with placebo. Due to small sample size, relative risk ratios with wide confidence intervals and concerns about external validity of the study the authors reported that conclusions could not be made to support the use of stiripentol as add-on treatment for focal refractory epilepsy. [98]

A Cochrane review of 6 RCTs (n=800) evaluating the effects of tiagabine add-on treatment in people with drug-resistant localisation-related seizures found that, compared with placebo, tiagabine reduces seizure frequency, but is associated with some adverse effects (overall study quality rated as high). [99]

A Cochrane review of 11 RCTs (1,401 participants) evaluating the effects of topiramate add-on treatment in people with drug-resistant partial epilepsy found that in the short-term, topiramate is three times more effective compared with placebo in reducing seizures; there was no evidence of long-term effects. It was noted that topiramate was associated with significantly more side-effects (moderate quality evidence). [100]

A Cochrane review of 5 RCTs (949 participants) evaluating the efficacy and tolerability of zonisamide add-on treatment for people with drug-resistant partial epilepsy found that zonisamide reduced seizure frequency compared with placebo (evidence had a low or unclear risk of bias). [101]

### 2014 surveillance summary

Three studies on the use of perampanel as an adjunctive treatment for the treatment of focal seizures in epilepsy were identified. The evidence suggested that compared with placebo, adjunctive treatment with perampanel 4–12 mg once daily reduces seizure frequency in people aged 12 years and older with uncontrolled focal seizures, but adverse events were high. [102-104] See Partial-onset seizures in epilepsy: perampanel as adjunctive treatment Evidence summary: new medicine (ESNM) 7.

### Topic expert feedback and additional information

As explained in the previous section (recommendation 1.9.1) concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline. In addition a topic expert said that recommendations concerning the use of sodium valproate (in relation to consent to treatment) should be considered for an update.

It was also noted that there are several new antiepileptic drugs since the revision in 2012 that should be considered for an update.

Topic experts highlighted the following studies:

- Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials and Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial.
Initial intelligence gathering identified that there are two Cochrane review protocols published investigating Perampanel add-on for drug-resistant partial epilepsy and Perampanel monotherapy for epilepsy. There is also a technology appraisal scheduled on Perampanel (Fycompa; E-2007; ER-155055-90) for Partial onset seizures with or without secondarily generalised seizures or primary generalised tonic clonic seizures in paediatric patients aged 4-12 with epilepsy – adjuvant treatment (TSID 9149).

Initial intelligence gathering identified that within Partial seizures in children and young people with epilepsy: zonisamide as adjunctive therapy (March 2014) ESNM37 it states that in October 2013, the approved licence for zonisamide (Zonegran, Eisai Limited; adjunctive treatment of partial seizures, with or without secondary generalisation, in adults) was extended to include ‘adolescents’ and children aged 6 years and over (see the European public assessment report (EPAR) for Zonegran).

Partial-onset seizures in epilepsy: zonisamide as monotherapy (April 2013) ESNM17 states that in June 2012, the approved licence for zonisamide (Zonegran; adjunctive treatment of partial seizures, with or without secondary generalisation, in adults) was extended to include monotherapy for treating partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy.

On-going research, Trial comparing the effectiveness and cost effectiveness of levetiracetam and zonisamide versus standard treatments for epilepsy: a comparison of Standard and New Antiepileptic Drugs (SANAD-II trial) was also identified. This study will provide updated effectiveness information for a range of AEDs. A topic expert also stated that the recommendations for levetiracetam needed review in terms of cost-effectiveness. It has been noted that the current price of levetiracetam is approximately half of the price in 2011, but as it is a category M in the Drug Tariff, prices can vary.

The publication from NIHR (National Institute for Health Research) A range of anti-epilepsy drugs are effective as first-line treatment was identified that concluded that ‘the findings support NICE recommendations to use carbamazepine or lamotrigine as first-line therapies for epilepsy with partial seizures, with levetiracetam as an alternative. Sodium valproate or lamotrigine are recommended for people with generalised tonic-clonic seizures, and levetiracetam is an alternative option.

Impact statement
Evidence identified in this surveillance review support the effectiveness of sodium valproate. However, safety concerns about sodium valproate in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see section on recommendation 1.9.1). The ongoing SANADII study will supply additional information and it is expected that data will be available during the update of the guideline.

The new evidence supports the current recommendations concerning the effectiveness of carbamazepine, lamotrigine, levetiracetam, oxcarbazepine as first-line treatments in children, young people and adults with newly diagnosed focal seizures. There was also evidence indicating that phenytoin may be an effective first-line treatments in people with newly diagnosed focal seizures, as this is not currently recommended, the evidence base for this AED should be reviewed as part of the guideline update. Other AEDs that have been assessed for effectiveness as first-line treatments in people with newly diagnosed focal seizures, that are also not currently recommended, are pregabalin, vigabatrin or clobazam, however there was only limited evidence of effectiveness of these AEDs and as such it is unlikely that this evidence would have an impact on the current recommendation.

There are several new AEDs (zonisamide, losigamone, brivaracetam and perampanel)
with evidence of effectiveness in the treatment of focal seizures; and indications that there are additional AEDs that might be considered as first-line treatment (e.g. phenytoin).

ESNM17 states that zonisamide could offer an alternative to other anti-epileptic drugs that are currently recommended as first-line treatment in people with newly diagnosed focal seizures 'because of its different mechanism of action, once-daily dosing, and adverse event and interaction profiles (unlike some other anti-epileptic drugs, zonisamide is not thought to affect the pharmacokinetics of other medicines, such as oral contraceptives, through cytochrome P450-mediated mechanisms)'. Evidence concerning the use of zonisamide monotherapy for focal seizures should be considered in the update.

The new evidence supports the current recommendations concerning the use of vigabatrin, lacosamide, eslicarbazepine acetate, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate and zonisamide as adjunctive treatments for refractory focal seizures. The guideline does not recommend felbamate or stiripentol as adjunctive treatments and current evidence does not indicate that this would change. The evidence concerning the effectiveness and safety profile of losigamone and brivaracetam (which are not currently recommended) as an adjunctive treatment for focal seizures could be considered in an update, however losigamone is not currently available in the UK.

Evidence concerning the use of perampanel as a first-line and adjunctive treatment should be considered during the update of this section.

Currently within NICE guideline CG137 when zonisamide is recommended, the footnote states that 'at the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented.' Appendix E provides information on each drug; for zonisamide: 'At the time of publication, zonisamide did not have UK marketing authorisation for use in children younger than 18 years owing to insufficient data on safety and efficacy (SPC). This is now not the case, at least for adjunctive treatment of partial seizures, with or without secondary generalisation; hence it is recommended that the footnote for recommendation 1.9.3.5 should be removed and reference to ESNM37 added (editorial correction). The change in licensing does not change the recommendation content.

**New evidence identified that may change current recommendations.**

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**Recommendations in this section of the guideline**

1.9.4 Pharmacological treatment of newly diagnosed generalised tonic-clonic (GTC) seizures

1.9.4.1 Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed GTC seizures. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.4.2 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]

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

Adjunctive treatment in children, young people and adults with GTC seizures
1.9.4.4 **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 1.9.4.1, 1.9.4.2 and 1.9.4.3) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10). [new 2012]

1.9.4.5 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]

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

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Pharmacological treatment of newly diagnosed generalised tonic-clonic (GTC) seizures

2018 surveillance summary

A Cochrane review of IPD from 595 of 1,192 eligible participants from 4 of 12 RCTs assessed the time to withdrawal, 6 and 12 month remission, and first seizure with carbamazepine compared to phenytoin, used as monotherapy in people with partial onset or generalised tonic-clonic seizures, with or without other generalised seizure types. It found no evidence for a statistically significant difference between carbamazepine and phenytoin for these outcomes, but the authors noted that CIs were wide and they could not exclude the possibility of important differences. There was evidence of more serious adverse events with phenytoin than carbamazepine. While there was some evidence that people with generalised seizures may be less likely to withdraw early from phenytoin than from carbamazepine, misclassification of seizure type may have impacted upon the results (the authors identified up to 48 individuals with misclassification of seizure type, 32% of whom had generalised epilepsy). The review authors recommend caution when interpreting the results of this review, and do not recommend that our results alone should be used in choosing between carbamazepine and phenytoin'. [78]

A Cochrane review undertook an IPD analysis incorporating a network meta-analysis (NMA). Data was available from 12,391 of 17,961 eligible participants from 36 of 77 RCTs. The analysis compared the time to withdrawal of allocated treatment, remission and first seizure of 10 AEDs that are currently used as monotherapy in children and adults with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus). The results indicate that carbamazepine and lamotrigine are suitable first-line treatments for individuals with partial onset seizures and that levetiracetam may be a suitable alternative. There was high-quality evidence supporting the use of sodium valproate as the first-line treatment for individuals with generalised tonic-clonic seizures (with or without other generalised seizure types) and that lamotrigine and levetiracetam would be suitable alternative first-line treatments. [80]

A Cochrane review of IPD available for 1,151 of 1,239 eligible participants from 2 of 3 RCTs evaluated the effects of topiramate monotherapy versus carbamazepine monotherapy for epilepsy in people with partial-onset seizures or generalised onset tonic-clonic seizures. It reported that with
carbamazepine 12-month remission is achieved earlier and it is less likely to be withdrawn than topiramate in individuals with partial-onset seizures. While evidence indicated no differences between the drugs and outcomes in people with generalised-onset tonic-clonic seizures, there were only a limited number of individuals identified with these seizures (15% of the sample). [81]

A Cochrane review of IPD available for 2,572 of 3,394 eligible participants from 9 of 13 RCTs evaluated the effectiveness of lamotrigine monotherapy compared to carbamazepine monotherapy in people with partial onset seizures or generalised onset tonic-clonic seizures. It reported that in individuals with partial onset seizures lamotrigine was significantly less likely to be withdrawn than carbamazepine, but carbamazepine may be superior in terms of seizure control. The results were less clear for individuals with generalised onset seizures, who made up only 12% of cases, as the study authors were concerned that seizure type may have been misclassified in up to 50% of these participants. Methodological quality of the studies was generally good. [82]

A Cochrane review of IPD available for 836 of 1,455 eligible participants from 6 of 13 RCTs evaluated pair-wise monotherapy comparisons in people with partial onset seizures or generalised onset tonic-clonic seizures. It reported that carbamazepine may be more effective than phenobarbitone in terms of seizure control and adverse events; and that for time to first seizure recurrence phenobarbitone was better for partial seizures and carbamazepine for generalised seizures. The evidence was rated as low quality. [83]

A Cochrane review of 2 RCTs/quasi RCTs (163 participants) evaluating the efficacy, effectiveness, tolerability and safety of clobazam as monotherapy in people with new-onset partial or generalised seizures found ‘no advantage for clobazam over carbamazepine for still taking treatment (retention) at 12 months in drug-naive children and a slight advantage of clobazam over phenytoin for retention at six months in adolescents and adults with neurocysticercosis’. [84]

A Cochrane review of IPD available for 480 of 517 eligible participants from 3 RCTs compared oxcarbazepine and phenytoin monotherapy in participants with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types. It reported that there was a statistically significant advantage for oxcarbazepine over phenytoin for time to treatment withdrawal, but insufficient evidence to suggest a difference between the drugs for other outcomes. By seizure type, there was no significant advantage for either drug for generalised epilepsy, however oxcarbazepine is significantly less likely to be withdrawn than phenytoin in participants with partial onset seizures, but it was not possible to determine whether oxcarbazepine is equivalent, superior or inferior to phenytoin in terms of seizure control. [86]

A Cochrane review of IPD available for 669 of 1,119 eligible participants from 5 of 11 RCTs investigated the time to withdrawal, remission and first seizure of phenytoin compared to valproate when used as monotherapy in people with partial onset seizures or generalised tonic-clonic seizures (with or without other generalised seizure types). It reported no overall difference between the drugs for these outcomes, nor any statistical interaction between treatment and seizure type. The authors noted that ‘misclassification of seizure type may have confounded the results of this review’ and that ‘no outright evidence was found to support or refute current treatment policies’. [87]

A Cochrane review of IPD available for 599 eligible participants from 4 of 8 RCTs evaluated the effectiveness of phenobarbitone monotherapy versus phenytoin monotherapy in children or adults with partial onset seizures or generalised onset tonic-clonic seizures. It found no significant differences for seizure outcomes between the 2 AEDs, but a
statistically significant clinical advantage for phenytoin in terms of treatment withdrawal (the authors hypothesised that phenobarbitone may lead to more adverse effects). The substantial statistical heterogeneity between studies and lack of blinding in two studies may have confounded the results. [88]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
As discussed previously (see recommendation 1.9.1) concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline. In addition, topic experts noted that recommendation 1.9.4.1 may need to be revised or re-worded due to new data and changes in policy concerning the use of sodium valproate in treating girls and women with epilepsy.

On-going research, Trial comparing the effectiveness and cost effectiveness of levetiracetam and zonisamide versus standard treatments for epilepsy: a comparison of Standard and New Antiepileptic Drugs (SANAD-II trial) was also identified (see recommendation 1.9.3).

Impact statement
This section of the guideline should be updated. The new evidence supports the current recommendations concerning the effectiveness of lamotrigine, carbamazepine and oxcarbazepine as first-line treatments in children, young people and adults with newly diagnosed generalised tonic–clonic (GTC) seizures.

While evidence identified in this surveillance review also supports the effectiveness of sodium valproate, safety concerns about its use in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see section on recommendation 1.9.1).

There is also evidence to support the use of clobazam, levetiracetam and topiramate monotherapy in treating GTC seizures. The new evidence concerning the effectiveness of phenytoin (not currently recommended) as a treatment in children, young people and adults with GTC seizures should be considered during the update of this section.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.5 Pharmacological treatment of absence seizures

First-line treatment in children, young people and adults with absence seizures

1.9.5.1 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

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

Adjunctive treatment in children, young people and adults with absence seizures

1.9.5.3 If two first-line AEDs (see recommendations 1.9.5.1 and 1.9.5.2) 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[15] or sodium
valproate. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.5.4 If adjunctive treatment (see recommendation 1.9.5.3) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clonazepam**; clonazepam, levetiracetam**, topiramate** or zonisamide**. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.
** At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented.

Pharmacological treatment of absence seizures

2018 surveillance summary

A Cochrane review of 8 RCTs (n=684 evaluated the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures, when compared with either placebo or each other. The review authors suggested that ethosuximide was the best initial empirical monotherapy but valproate may be more appropriate, if absence and generalised tonic-clonic seizures coexist as ethosuximide is less effective for management of tonic-clonic seizures. [105]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback and additional information

As discussed previously (see recommendation 1.9.1) concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline. In addition, a topic expert indicated that recommendation 1.9.5.1 may need to be revised or re-worded due to new data and changes in policy concerning the use of sodium valproate in treating girls and women with epilepsy.

Impact statement

The new evidence supports the recommendation content within 1.9.5.1-1.9.5.3. However safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see section on recommendation 1.9.1).

Recommendations in this section of the guideline

1.9.6 Pharmacological treatment of myoclonic seizures

First-line treatment in children, young people and adults with myoclonic seizures
1.9.6.1 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.6.2 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]

Adjunctive treatment in children, young people and adults with myoclonic seizures

1.9.6.3 Offer levetiracetam, sodium valproate or topiramate** as adjunctive treatment to children, young people and adults with myoclonic seizures if first-line treatments (see recommendations 1.9.6.1 and 1.9.6.2) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.6.4 If adjunctive treatment (see recommendation 1.9.6.3) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam**, clonazepam, piracetam or zonisamide**. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

Pharmacological treatment of myoclonic seizures

2018 surveillance summary

No relevant evidence was identified.

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback and additional information

Concerns about the safety of sodium valproate treatment in girls and women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1). A topic expert also indicated that recommendation 1.9.6.1 may need to be revised or re-worded due to new data and changes in policy concerning the use of sodium valproate in treating girls and women with epilepsy.

Impact statement

Safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see discussion in section on recommendation 1.9.1).

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.7 Pharmacological treatment of tonic or atonic seizures

First-line treatment in children, young people and adults with tonic or atonic seizures
1.9.7.1 Offer sodium valproate as first-line treatment to children, young people and adults with tonic or atonic seizures. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

Adjunctive treatment in children, young people and adults with tonic or atonic seizures

1.9.7.2 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]

1.9.7.3 Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 1.9.7.2) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide** and topiramate**. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

Pharmacological treatment of tonic or atonic seizures

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback
Concerns about the safety of sodium valproate treatment in girls and women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1). A topic expert also indicated that recommendation 1.9.7.1 may need to be revised or re-worded due to new data and a change in policy concerning the use of sodium valproate in treating girls and women with epilepsy.

Impact statement
Safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see discussion in section on recommendation 1.9.1).

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.8 Pharmacological treatment of infantile spasms
First-line treatment in infants with infantile spasms
1.9.8.1 Discuss with, or refer to, a tertiary paediatric epilepsy specialist when an infant presents with infantile spasms. [new 2012]
1.9.8.2 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]

1.9.8.3 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]

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

Pharmacological treatment of infantile spasmss

2018 surveillance summary

A Cochrane review of RCTs of add-on sulthiame in people of any age with any type of epilepsy found only 1 study: participants with a new diagnosis of West syndrome (n=37) given sulthiame as an add-on therapy to pyridoxine. Sulthiame led to a cessation of seizures. The included study had a significant risk of bias. [106]

A Cochrane review that included 1 randomised control cross-over trial (5 participants) evaluating the efficacy and tolerability of corticosteroids compared to placebo or other antiepileptic drugs in children with epilepsy (excluding epileptic spasms) found no new evidence for the efficacy of corticosteroids in treating childhood epilepsies. [107]

A Cochrane review of 18 RCTs (916 participants with infantile spasms) investigated 12 different pharmaceutical agents. The strongest evidence suggesting that hormonal treatment (prednisolone or tetracosactide depot) leads to resolution of spasms faster and in more infants than does vigabatrin (overall poor study methodology). [108]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts identified Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Topic experts said that recommendation 1.9.8.2 should be updated in relation to evidence on the use of a combination of vigabatrin and prednisolone.

Impact statement

This section of the guideline should be updated. The new evidence from Cochrane reviews [107, 108] supports the recommendations for offering prednisolone or tetracosactide as a treatment for infantile spasms, however a recent large international study published in 2017 demonstrated that the combination of vigabatrin and prednisolone was more effective than either oral prednisolone or intramuscular tetracosactide used alone in completely suppressing infantile spasms in the short-term (42 days). There is also an indication that sulthiame, which is not currently recommended in NICE guideline CG137, may lead to a cessation of seizures when used as an add-on therapy to pyridoxine in patients with West syndrome, however the review was based on only 1 small study with a significant risk of bias [106].

New evidence identified that may change current recommendations.
Recommendations in this section of the guideline

1.9.9 Pharmacological treatment of Dravet syndrome

First-line treatment in children with Dravet syndrome

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

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

Adjunctive treatment in children, young people and adults with Dravet syndrome

1.9.9.3 Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 1.9.9.2) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam* or stiripentol as adjunctive treatment. [new 2012]

1.9.9.4 Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. [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 E for details). Informed consent should be obtained and documented.

Pharmacological treatment of Dravet syndrome

2018 surveillance summary

A Cochrane review of 2 RCTs (64 participants) evaluating the effectiveness and tolerability of stiripentol in children with severe myoclonic epilepsy in infants (Dravet syndrome) found that it is significantly better than placebo for achieving 50% or greater reduction in seizure frequency and seizure freedom, but there were more adverse effects. Quality of the evidence was rated as low to moderate. [109]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback and additional information

A topic expert noted that there should be recommendations on the use of cannabidiol in children with refractory epilepsy, ‘as parents will often obtain this independently and there is much confusion surrounding its use, legality, safety and efficacy’. Topic experts highlighted evidence concerning the use of cannabidiol in infants with Dravet syndrome: Cannabidiol

(CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial reported that ‘CBD resulted in greater reduction in seizure frequency than placebo; adverse events were more frequent with CBD, but it was generally well-tolerated’ (there is a second publication in the New England Journal of Medicine which reports the same data).

Initial intelligence gathering identified the proposed NICE technology appraisal (TA) Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome that will appraise the clinical and cost effectiveness of cannabidiol within its marketing authorisation for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome.

As discussed previously, NICE's concerns about the safety of sodium valproate treatment in girls and women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1).

Impact statement

New evidence supports the current recommendation concerning use of stiripentol in children with Dravet syndrome. There is
evidence on the use of cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome and a planned NICE TA in this area. An editorial correction will need to be made cross-referencing to the NICE TA on Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial when published (if development of the TA is agreed).

Safety concerns about sodium valproate in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies (see section on recommendation 1.9.1).

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.10 Pharmacological treatment of Lennox–Gastaut syndrome

First-line treatment in children with Lennox–Gastaut syndrome

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

1.9.10.2 Offer sodium valproate as first-line treatment to children with Lennox–Gastaut syndrome. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

Adjunctive treatment in children, young people and adults with Lennox–Gastaut syndrome

1.9.10.3 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]

1.9.10.4 Discuss with a tertiary epilepsy specialist if adjunctive treatment (see recommendation 1.9.10.3) is ineffective or not tolerated. Other AEDs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. [new 2012]

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

1.9.10.6 Only offer felbamate** in centres providing tertiary epilepsy specialist care and when treatment with all of the AEDs listed in recommendations 1.9.10.3 and 1.9.10.4 has proved ineffective or not tolerated. [new 2012]

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

Pharmacological treatment of Lennox–Gastaut syndrome

2018 surveillance summary

A Cochrane review of 9 RCTs (n=979) evaluating the effects of pharmaceutical therapies used to treat Lennox-Gastaut syndrome reported that rufinamide, lamotrigine, topiramate and felbamate may be helpful as add-on therapy, and clobazam may be helpful for drop seizures; however the optimum treatment is unknown, and none of
the studies has shown any one drug to be highly efficacious. [110]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

NICE’s concerns about the safety of sodium valproate treatment in girls and women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).

Initial intelligence gathering identified the in-development NICE technology appraisal (TA) Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome that will appraise the clinical and cost effectiveness of cannabidiol within its marketing authorisation for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome. A TA is also proposed on Cannabidiol for Lennox-Gastaut syndrome in paediatric and adult patients with treatment-resistant seizures.

Impact statement
The new evidence supports the current recommendation to offer rufinamide, lamotrigine, topiramate or felbamate as adjunctive treatment for people with Lennox-Gastaut syndrome. Evidence for potential effectiveness of clobazam should be reviewed in an update.

Safety concerns about sodium valproate in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies.

An editorial correction will need to be made cross-referencing to the NICE TA on Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial when it is published.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

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

First-line treatment in children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type)

1.9.11.1 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]

1.9.11.2 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]

1.9.11.3 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 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10). [new 2012]

1.9.11.4 Consider adjunctive treatment if a second well-tolerated AED is ineffective (see recommendations 1.9.11.2 and 1.9.11.3). [new 2012]

Adjunctive treatment in children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type)

1.9.11.5 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 1.9.11.2 and 1.9.11.3) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10). [new 2012]

1.9.11.6 If adjunctive treatment (see recommendation 1.9.11.5) 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]

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E 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.

† February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

2018 surveillance summary

A Cochrane review of 4 RCTs (262 participants) assessing the outcome of treatment with AEDs in children with Benign Epilepsy with Centro Temporal Spikes (BECTS), reported that the studies were of low to very low quality and that there were no differences in seizure remission at the end of the study periods between the AEDs compared (levetiracetam versus oxcarbazepine; clobazam versus carbamazepine; carbamazepine versus topiramate); but 1 placebo-controlled trial with a low risk of bias, found that children with BECTS on sulthiame were significantly more likely to remain in seizure remission in the short-term (up to 6 months), although the precision of the effect estimate was uncertain due to its small sample size. [111]

2014 surveillance summary

No relevant evidence was identified.

Topic expert feedback and additional information

No topic expert feedback was relevant to this evidence.

Concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).
Impact statement

This section of the guideline should be updated. Evidence concerning the effectiveness of sulthiame as a treatment in children with Benign Epilepsy with Centro Temporal Spikes should be considered in the update.

Safety concerns about sodium valproate treatment in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.12 Pharmacological treatment of idiopathic generalised epilepsy (IGE)

First-line treatment in children, young people and adults with IGE

1.9.12.1 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.12.2 Offer lamotrigine** if sodium valproate is unsuitable or not tolerated. Be aware that lamotrigine can exacerbate myoclonic seizures. If JME is suspected see recommendations 1.9.13.1 and 1.9.13.2. [new 2012]

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

Adjunctive treatment in children, young people and adults with IGE

1.9.12.4 Offer lamotrigine**, levetiracetam**, sodium valproate or topiramate** as adjunctive treatment to children, young people and adults with IGE if first-line treatments (see recommendations 1.9.12.1, 1.9.12.2 and 1.9.12.3) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.12.5 If adjunctive treatment (see recommendation 1.9.12.4) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam**, clonazepam or zonisamide**. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

** At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented.
Pharmacological treatment of idiopathic generalised epilepsy (IGE)

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

Concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).

Impact statement
This section of the guideline should be updated as safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.13 Pharmacological treatment of juvenile myoclonic epilepsy (JME)

First-line treatment in children, young people and adults with JME

1.9.13.1 Offer sodium valproate as first-line treatment to children, young people and adults with newly diagnosed JME, unless it is unsuitable. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.13.2 Consider lamotrigine[^15], levetiracetam[^15] or topiramate[^15] 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]

Adjunctive treatment in children, young people and adults with JME

1.9.13.3 Offer lamotrigine[^15], levetiracetam, sodium valproate or topiramate[^15] as adjunctive treatment to children, young people and adults with JME if first-line treatments (see recommendations 1.9.13.1 and 1.9.13.2) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)[^14], [new 2012]

1.9.13.4 If adjunctive treatment (see recommendation 1.9.13.3) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam[^15], clonazepam or zonisamide[^15]. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

** At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented.
Pharmacological treatment of juvenile myoclonic epilepsy (JME)

2018 surveillance summary
A Cochrane review of 3 RCTs (83 participants) evaluating the efficacy and tolerability of topiramate monotherapy in the treatment of juvenile myoclonic epilepsy found that a greater proportion of participants in the topiramate group had a 50% or more reduction in primarily generalised tonic-clonic seizures (PGTCS) compared with the placebo group, there were no significant differences between topiramate versus valproate in participants responding with a 50% or more reduction in myoclonic seizures or in PGTCS or seizure-free; adverse events associated with topiramate were ranked as moderate-to-severe, while 59% of adverse events linked to valproate were ranked as severe and systemic toxicity scores were higher in the valproate compared to topiramate group. Quality of the evidence was very low. [112]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

Concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).

Impact statement
This section of the guideline should be updated. Safety concerns about sodium valproate in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies. While the authors of the Cochrane review concluded that there was insufficient evidence to support topiramate for the treatment of people with JME, 'based on the current limited available data, topiramate seems to be better tolerated than valproate'. The new evidence indicates that topiramate may have a more favourable side-effect profile than sodium valproate, as such recommendation 1.9.13.2 which says that topiramate has a less favourable side-effect profile than sodium valproate, may need to be reconsidered (but evidence was considered as very low quality).

Recommendations in this section of the guideline
1.9.14 Pharmacological treatment of epilepsy with generalised tonic-clonic (GTC) seizures only
First-line treatment in children, young people and adults with epilepsy with GTC seizures only
1.9.14.1 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]
1.9.14.2 Consider carbamazepine and oxcarbazepine** but be aware of the risk of exacerbating myoclonic or absence seizures. [new 2012]

Adjunctive treatment in children, young people and adults with epilepsy with GTC seizures only
1.9.14.3 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 recommendations 1.9.14.1 and 1.9.14.2) are ineffective or not tolerated. Be aware of the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

Pharmacological treatment of epilepsy with generalised tonic–clonic (GTC) seizures only

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

Concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).

Impact statement
This section of the guideline should be updated as safety concerns about sodium valproate in women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies.

New evidence identified that may change current recommendations.

Recommendations in this section of the guideline

1.9.15 Pharmacological treatment of childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes

First-line treatment in children, young people and adults with childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes

1.9.15.1 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 the teratogenic and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

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

Adjunctive treatment in children, young people and adults with childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes

1.9.15.3 If two first-line AEDs (see recommendations 1.9.15.1 and 1.9.15.2) 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 and developmental risks of sodium valproate (see recommendation 1.9.1.10)*. [new 2012]

1.9.15.4 If adjunctive treatment (see recommendation 1.9.15.3) is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam**, clonazepam, levetiracetam**, topiramate** or zonisamide**. [new 2012]

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

* February 2016: see also the MHRA toolkit on the risks of valproate medicines in female patients.

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

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**Pharmacological treatment of childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes**

**2018 surveillance summary**

No relevant evidence was identified.

**2014 surveillance summary**

No relevant evidence was identified.

**Topic expert feedback and additional information**

No topic expert feedback was relevant to this evidence.

Concerns about the safety of sodium valproate treatment in women have triggered this exceptional review and potential update of the guideline (see recommendation 1.9.1 for discussion of these issues).

**Impact statement**

This section of the guideline should be updated as safety concerns about sodium valproate in girls and women have suggested the need to review the recommendations for sodium valproate and its place in the management of the epilepsies.

New evidence identified that may change current recommendations.

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**Recommendations in this section of the guideline**

**1.9.16 Other epilepsy syndromes**

**1.9.16.1** 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-atonic epilepsy. [new 2012]

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**Other epilepsy syndromes**

**2014 surveillance summary**

No relevant evidence was identified.
Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The absence of new evidence indicates no need to update this section of the guideline.

No new evidence. Recommendations are unlikely to change.

Recommendations in this section of the guideline

1.9.17 Continuation of pharmacological treatment

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

1.9.17.2 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]

1.9.17.3 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]

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

1.9.17.5 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]

1.9.17.6 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 1.2)
- using simple medication regimens
- positive relationships between healthcare professionals, the child, young person or adult with epilepsy and their family and/or carers. [2004]

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

1.9.17.8 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]

1.9.17.9 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 1.15.3.19). [2012]

1.9.17.10 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]

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

* 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.

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

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**Continuation of pharmacological treatment**

**2018 surveillance summary**

A Cochrane review of 12 RCTs/quasi-RCTs (1,642 participants) assessing the effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy, found that education and counselling of participants with epilepsy resulted in mixed success (moderate-quality evidence), behavioural interventions such as the use of intensive reminders led to more favourable effects (moderate-quality evidence) and mixed interventions showed improved adherence in the intervention groups compared to the control groups (high-quality evidence). [113]

**2014 surveillance summary**

No relevant evidence was identified.

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**Topic expert feedback and additional information**

No topic expert feedback was relevant to this evidence.

Intelligence gathering identified in-development NICE guideline Behaviour change: technology-based interventions which may cover medication e-reminders (draft scope not currently available).

**Impact statement**

This section of the guideline should be updated. There is new evidence that indicates behavioural interventions such as intensive medication reminders can be good at improving adherence (more so than educational interventions), but these are not currently recommended within rec 1.9.17.6 on adherence.

New evidence identified that may change current recommendations.

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**Recommendations in this section of the guideline**

**1.9.18 Withdrawal of pharmacological treatment**
1.9.18.1 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]

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

1.9.18.3 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 of the full guideline). [2004]

1.9.18.4 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]

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

1.9.18.6 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]

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

Withdrawal of pharmacological treatment

2018 surveillance summary
A Cochrane review of 5 RCTs (924 participants) assessed the risk of seizure recurrence, status epilepticus and mortality after early and late AED discontinuation in adult and paediatric epilepsy patients. Only studies with children (aged under 16 years old) were found. The studies indicated that AEDs should not be discontinued in children until after at least two seizure-free years, particularly if individuals have an abnormal EEG (especially epileptiform activity) or partial seizures, or both. There was insufficient evidence to establish when to withdraw AEDs in children with generalised seizures. The included trials were classified as low or unclear risk of bias. [114]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence supports recommendation 1.9.18.3, that withdrawing AED therapy should only be considered when seizure free for at least 2 years; however there is only evidence for this in children, there is a lack of evidence in adults and in children with generalised seizures. The recommendation does not highlight any potential concerns in withdrawing AEDs for these populations.

New evidence is unlikely to change guideline recommendations.
1.10 Referral for complex or refractory epilepsy

Recommendations in this section of the guideline

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

1.10.2 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]

1.10.3 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]

1.10.4 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]

1.10.5 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]

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

1.10.7 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]

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

1.10.9 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]
1.10.10 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]

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

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
A RCT found that surgery improved patient outcomes (freedom from disabling seizures) in patients who had failed on 2 AEDs compared to continued AED. Patients in the surgery group also had a greater increase in HRQoL than those in the drug-treatment group up to 1.5yrs following surgery. [115]

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

Deep brain stimulation for refractory epilepsy (January 2012) IPG416 states that 'the evidence on the efficacy of deep brain stimulation (DBS) for refractory epilepsy is limited in both quantity and quality. The evidence on safety shows that there are serious but well-known side effects. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.'

Impact statement
The evidence is consistent with the recommendation in NICE guideline CG137 that patients whose epilepsy is not controlled with medication within 2 years or after trying 2 drugs should be assessed for epilepsy surgery. Reference to IPG416 should be considered.

New evidence is unlikely to change guideline recommendations.

1.11 Psychological interventions

Recommendations in this section of the guideline

1.11.1 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]

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

1.11.3 Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment. [2004]
2018 surveillance summary
A Cochrane review of 24 RCTs/quasi-RCTs (2,439 participants) assessing the effects of psychological treatments for people with epilepsy on quality of life (QoL) outcomes, with a meta-analysis based on data from 9 studies (468 participants), found that self-management interventions significantly improved QoL and emotional well-being, and reduced fatigue in adults and adolescents with epilepsy. The evidence was of moderate quality. [116]

A Cochrane review of studies (RCTs, quasi-RCTs, prospective cohort controlled studies, and prospective before-and-after studies) that aimed to identify and assess possible psychological and neuropsychological interventions for adults with newly diagnosed epilepsy found 2 RCTs, 1 on a cognitive behavioural intervention in adolescents (low quality evidence) which reported that the intervention significantly reduced depressive symptoms in people with subthreshold depressive disorder; and 1 on a specialist nurse intervention in adults (very low quality evidence) which reported no significant benefit for depressive symptoms. [117]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The guideline makes broad recommendations concerning interventions to improve psychological difficulties associated with epilepsy including recommending relaxation and cognitive behaviour therapy; and recognises the psychological impact of epilepsy and that it should be identified and addressed. The evidence supports the current recommendation, and the findings of the most recent Cochrane review [116] may provide additional intervention details that could be reflected in the recommendation content. This section of the guideline should be updated.

New evidence identified that may change current recommendations.

1.12 Ketogenic diet

Recommendations in this section of the guideline

1.12.1 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]

2018 surveillance summary
A Cochrane review of 7 RCTs (427 participants) evaluating the efficacy and tolerability of ketogenic diet and ‘similar diets’ for people with epilepsy found no studies with adults, all participants were children or adolescents. There was some evidence for greater antiepileptic efficacy for a 4:1 ketogenic diet over lower ratios, but the 4:1 ketogenic diet was consistently associated with more adverse effects; and adverse effects were often the reason for participants dropping out of trials (other reasons included lack of efficacy and non-acceptance of the diet). While the results for the use of ketogenic
diet in epilepsy are described as ‘promising’, the evidence was poor quality. [118]

2014 surveillance summary
One RCT in India investigated the efficacy of the modified Atkins diet compared to a normal diet in children with refractory epilepsy. Mean seizure frequency was lower in children on the modified Atkins diet compared with the control group. However, this non blinded study included a large proportion of vegetarian children, which may not be mirrored in UK children. [119]

Topic expert feedback
Topic experts identified an on-going RCT investigating ketogenic diet in the treatment of epilepsy in children under the age of 2 years. And a topic expert said that the evidence for the benefit of ketogenic diet in adults with severe refractory epilepsy should be reviewed, highlighting the Cochrane review identified in the search [118].

Impact statement
New evidence is unlikely to impact on guideline recommendations due to limitations in study design and lack of sufficient evidence.

New evidence is unlikely to change guideline recommendations.

1.13 Vagus nerve stimulation (VNS)

Recommendations in this section of the guideline

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

1.13.2 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]

* 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.


2018 surveillance summary
A Cochrane review of 5 RCTs (439 participants) evaluating the effects of vagus nerve stimulation (VNS) on seizures in adults or children with drug-resistant partial seizures and who are not eligible for surgery or who have failed surgery, found that VNS for partial seizures is effective and well tolerated. VNS stimulation using the high stimulation paradigm
was significantly better than low stimulation in reducing frequency of seizures. Adverse effects associated with implantation and stimulation were mainly 'hoarseness, cough, dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation' (evidence on these outcomes was limited and of moderate to low quality). [120]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
No topic expert feedback was relevant to this evidence.

On-going research on the French vagus nerve stimulation (VNS) epilepsy registry to guide physicians and their patients in the use of the VNS therapy for patients with epilepsy was identified.

Impact statement
This section of the guideline should be updated. Evidence indicates that for focal seizures VNS appears to be effective and well tolerated and that VNS stimulation using a high stimulation paradigm is significantly better than low stimulation in reducing frequency of seizures, however there was limited information available 'so important differences between high and low stimulation cannot be excluded'. VNS is recommended in the guideline for people with refractory epilepsy and focal seizures but there is no mention of low versus high stimulation, as such the evidence in the review may impact on the recommendation.

New evidence identified that may change current recommendations.

1.14 Prolonged or repeated seizures and convulsive status epilepticus

Recommendations in this section of the guideline

1.14.1 First-line treatment for children, young people and adults with prolonged or repeated generalised, convulsive (tonic–clonic, tonic or clonic) seizures in the community

1.14.1.1 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]

1.14.1.2 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]

1.14.1.3 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]

1.14.1.4 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]

1.14.1.5 Care must be taken to secure the child, young person or adult's airway and assess his or her respiratory and cardiac function. [2004]
1.14.1.6 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]

1.14.2 Treatment for children, young people and adults with convulsive status epilepticus in hospital

Convulsive status epilepticus

1.14.2.1 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 F. [new 2012]

1.14.2.2 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 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 F. [new 2012]

1.14.2.3 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 F. [new 2012]

Refractory convulsive status epilepticus

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

1.14.2.5 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 F. [new 2012]

1.14.2.6 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 F. [2012]

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

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

1.14.2.9 Regular AEDs should be continued at optimal doses and the reasons for status epilepticus should be investigated. [2004]
1.14.2.10 An individual treatment pathway should be formulated for children, young people and adults who have recurrent convulsive status epilepticus. [2004]

1.14.3 **Non-convulsive status epilepticus**

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

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details). Informed consent should be obtained and documented in line with normal standards in emergency care.

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**2018 surveillance summary**

A Cochrane review of 18 RCTs (2,755 participants) assessed the relative effectiveness and safety of anticonvulsants in status epilepticus reported that Intravenous (IV) lorazepam is better than IV diazepam or IV phenytoin alone for risk of non-cessation of seizures. The risk of continuation of status epilepticus requiring a different drug or general anaesthesia was lower with IV lorazepam than IV diazepam, but both IV lorazepam and diazepam were better than placebo for these outcomes. Although IV lorazepam was better than IV phenytoin for reducing risk of non-cessation of seizures, it was not clear whether IV valproate had any benefit over IV phenytoin. For pre hospital management, midazolam IM appeared more effective than lorazepam IV for control of seizures, frequency of hospitalisation and ICU admissions. However the Cochrane authors noted ‘it was unclear whether the risk of recurrence of seizures differed between treatments’. Because of the low numbers of studies and participants in each comparison, differences in adverse effects between anticonvulsants are unclear. The quality of included studies was acceptable but risk of bias could not be determined because of incomplete and selective reporting of data in the individual studies. [121]

A Cochrane review evaluating the efficacy, adverse effects, and short- and long-term outcomes of refractory status epilepticus (RSE) treated with one of the two anaesthetic agents: thiopental sodium or propofol only identified 1 RCT (24 participants) which was terminated early due to recruitment problems. It was not possible to determine the efficacy of propofol and thiopental sodium compared to each other in the treatment of RSE. [122]

**2014 surveillance summary**

A cohort study conducted in France using French protocols indicated that treating patients with generalised convulsive status epilepticus according to a guideline-based protocol improves outcomes. [123]

A systematic review which meta-analysed 3 small poor quality studies (based in India, Israel and China) compared intravenous sodium valproate with either intravenous phenytoin or IV diazepam in hospitalised patients with generalised convulsive status epilepticus was identified. No significant difference was observed between IV sodium valproate and IV phenytoin for seizure freedom at 24 hours or seizure cessation within 30 minutes of drug. Patients on IV sodium valproate were less likely to experience adverse effects than those on intravenous phenytoin. [124]

**Topic expert feedback**

Topic experts highlighted the importance of 2 on-going trials investigating treatment for children, young people and adults with convulsive status epilepticus in hospital: A pragmatic randomised controlled trial of intravenous levetiracetam versus intravenous phenytoin in terminating acute, prolonged tonic clonic seizures including convulsive status...
epilepticus in children, the 'EcLiPSE' Study: Emergency treatment with Levetiracetam or Phenytoin in Status Epilepticus and Convulsive Status Epilepticus Paediatric Trial (ConSEPT): A PREDICT study comparing levetiracetam versus phenytoin for management of convulsive status epilepticus in children.

Impact statement
The section on first-line treatment for children, young people and adults with prolonged or repeated generalised, convulsive seizures in the community should be updated. There is new evidence on the relative effectiveness and safety of anticonvulsants in status epilepticus, which indicates that intramuscular administration of midazolam is more effective than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions, however the authors reported that 'it was unclear whether the risk of recurrence of seizures differed between treatments.'[121] Evidence concerning midazolam IM should be considered in an update. The evidence concerning IV administration of lorazepam, diazepam and phenytoin is in line with current recommendations; however there are 2 important on-going trials investigating treatment for children, young people and adults with convulsive status epilepticus in hospital. Evidence concerning the use of anaesthetic agents is of low quality and unlikely to impact current recommendations.

New evidence identified that may change current recommendations.

1.15 Women and girls with epilepsy

Recommendations in this section of the guideline

1.15.1 Information and advice for women and girls with epilepsy
1.15.1.1 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]
1.15.1.2 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]
1.15.1.3 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]
1.15.1.4 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]
1.15.1.5 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]

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

1.15.1.7 Refer to the SPC and BNF for individual drug advice on the interactions between AEDs and hormonal replacement and contraception. [new 2012]

1.15.2 Contraception

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

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

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

1.15.2.4 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. [2004, amended 2012]

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

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

1.15.2.7 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]

1.15.2.8 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. [2004, amended 2012]

1.15.2.9 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]

1.15.3 Pregnancy

1.15.3.1 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 1.9.18). [2004]

1.15.3.2 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. [2004]

1.15.3.3 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]

1.15.3.4 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]
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]

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]

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]

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]

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

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]

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]

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

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

Although there is an increased risk of seizures in children of parents with epilepsy, 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]

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]

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

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

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]

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]

**Breastfeeding**

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]
1.15.2 Prescribers should consult individual drug advice in the SPC and the BNF** 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]

1.15.5 After the birth

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

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

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

* In this recommendation, ‘progesterone’ has been replaced with ‘progestogen’ to reflect a change in terminology since the original guideline was published in 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.

† Appendix D of the full guideline provides a checklist for the information needs of women and girls with epilepsy, and practical information for mothers with epilepsy.

2018 surveillance summary

A Cochrane review of prospective cohort controlled studies, cohort studies set within pregnancy registries and randomised controlled trials (50 studies with 31 contributing to meta-analysis) assessed the effects of prenatal exposure to AEDs on the prevalence of congenital malformations. Children exposed to valproate, carbamazepine or phenytoin were at a higher risk of malformation than children born to women without epilepsy and women with untreated epilepsy; children exposed to phenobarbital or topiramate were at a higher risk of malformation than children born to women without epilepsy. There was no increased risk for major malformation with lamotrigine. Gabapentin, levetiracetam, oxcarbazepine, primidone and zonisamide were not associated with an increased risk, but there were fewer data for these medications. When AEDs were compared, children exposed to valproate had the greatest risk of malformation, while levetiracetam and lamotrigine exposure carried the lowest risk of overall malformation; however, data pertaining to specific malformations are lacking. [125]

An earlier Cochrane review that included 22 prospective cohort studies and 6 registry based studies assessed the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes in children. Use of sodium valproate led to a reduction in IQ that was ‘sufficient to affect education and occupational outcomes in later life’. There may be a dose-relationship, with higher doses of sodium valproate (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child. However, it was also reported that for some women sodium valproate is the most effective drug at controlling seizures. There was insufficient data about the effects of the newer AEDs carbamazepine, lamotrigine and phenytoin. [126]
2014 surveillance summary

Two observational studies on the risks of sodium valproate on foetal development [127, 128], a cohort study on sodium valproate and the impact of folic acid use in reducing risks to foetal development [129], and a cohort study on the effects of breastfeeding during AED therapy on the cognitive outcomes of offspring [130] were identified. All findings were in line with current recommendations.

Topic expert feedback and additional information

Topic experts highlighted new advice from the MHRA around the use of sodium valproate for management of epilepsy, particularly in women of childbearing age. New data relates to accumulating observational data from a number of national and European Pregnancy Registries. These Registries report the outcomes of pregnancies of women with epilepsy, both treated and un-treated with all anti-epileptic drugs, with follow-up periods extending many years. These have shown a number of anti-epileptic drugs, but particularly sodium valproate, may be associated with foetal teratogenesis and developmental and cognitive impairments in children born to women taking these drugs at the time of conception and during pregnancy.

Initial intelligence gathering identified a publication from NIHR Links between antipsychotics in pregnancy and harmful outcomes for baby may be influenced by mother’s lifestyle which concluded that ‘studies highlight the serious adverse consequences for children exposed to valproate in pregnancy and reinforce the NICE guidance on avoiding prescribing valproate in childbearing aged women with mental disorders.’

Concerns about the safety of sodium valproate treatment in girls and women have triggered this exceptional review and potential update of the guideline (see discussion in section on recommendation 1.9.1).

Impact statement

This section of the guideline should be updated and re-evaluate the risks and benefits of sodium valproate treatment and reflect the warnings around treatment of girls and women. The evidence also indicates that while sodium valproate carries the highest risk of causing foetal malformation and developmental delay, other AEDs are associated with similar risks and this evidence should also be considered during the update.

New evidence identified that may change current recommendations.

1.16 Children, young people and adults with learning disabilities (see also sections 1.15 and 1.17)

Recommendations in this section of the guideline

1.16.1 Diagnosis (see also section 1.5)

1.16.1.1 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]

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

1.16.1.3 Clear, unbiased reporting is essential. Witnesses may need education to describe their observations accurately. [2004]
1.16.2 Investigations (see also section 1.6)

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

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

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

1.16.3 Management (see also section 1.8)

1.16.3.1 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]

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

1.16.3.3 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]

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

1.16.3.5 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]

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

1.16.3.7 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]

1.16.3.8 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]

2018 surveillance summary

A Cochrane review of 14 RCTs (1,116 participants) evaluated the efficacy of AEDs in people with epilepsy and intellectual disabilities. AEDs reduced seizure frequency in people with refractory epilepsy and intellectual disability and adverse events experienced by those with an intellectual disability were similar to those in the general population (low to moderate quality evidence). [131]
A Cochrane review evaluating non-pharmacological interventions for people with epilepsy and intellectual disabilities found only 1 RCT (n=NR; unclear risk of bias), which compared 2 surgical procedures: callosotomy with anterior temporal lobectomy versus anterior temporal lobectomy. Corpus callosotomy with anterior temporal lobectomy was more effective than anterior temporal lobectomy alone in improving quality of life and performance on IQ tests in people with epilepsy and intellectual disabilities but no evidence was found to support superior benefit in seizure control for either intervention. [132]

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback and additional information
A topic expert advised that people with a learning disability may face issues in rural settings around lack of accessible point of access for specialist services or specialist nursing support.

On-going research on Epilepsy nurse trial for adults with intellectual disabilities was identified.

Impact statement
The evidence is in line with current recommendations concerning pharmacological treatment in people with epilepsy and intellectual disabilities; and evidence on non-pharmacological treatments found no difference between different surgical procedures on outcomes. New evidence is unlikely to change guideline recommendations.

1.17 Young people with epilepsy (see also section 1.15)

Recommendations in this section of the guideline

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

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

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

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

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

1.17.6 Before the transition to adult services is made, diagnosis and management should be reviewed and access to voluntary organisations, such as support groups and epilepsy charities, should be facilitated. [2004]
1.17.7 The information given to young people should cover epilepsy in general and its diagnosis and treatment, the impact of seizures and adequate seizure control, treatment options including side effects and risks, and the risks of injury. Other important issues to be covered are the possible consequences of epilepsy on lifestyle and future career opportunities and decisions, driving and insurance issues, social security and welfare benefit issues, sudden death and the importance of adherence to medication regimes. Information on lifestyle issues should cover recreational drugs, alcohol, sexual activity and sleep deprivation (see section 1.3). [2004]

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

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**2018 surveillance summary**
No relevant evidence was identified.

**Impact statement**
The absence of new evidence indicates that there is no need to update this section of the guideline.

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**Topic expert feedback**
No topic expert feedback was relevant to this evidence.

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### 1.18 Older people with epilepsy

**Recommendations in this section of the guideline**

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

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

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**2018 surveillance summary**
A Cochrane review of 1 RCT (95 participants) evaluating the efficacy and tolerability of the treatment of epilepsy for people with Alzheimer’s disease did not find sufficient evidence to support levetiracetam, phenobarbital or lamotrigine for the treatment of epilepsy in people with Alzheimer’s disease (very low quality evidence). [133]

**2014 surveillance summary**
No relevant evidence was identified.
**Topic expert feedback**

Topic experts said there should be a focus on treatment of epilepsy in the elderly, including atypical seizures in the very elderly and which AED to use in those with dementia.

**Impact statement**

The evidence is in line with the recommendation to consider the potential impact of polypharmacy and comorbidity in older people with epilepsy.

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**1.19 Children, young people and adults from black and minority ethnic groups**

**Recommendations in this section of the guideline**

1.19.1 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]

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

1.19.3 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]

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**2018 surveillance summary**

No relevant evidence was identified.

**Impact statement**

The absence of new evidence indicates that there is no need to update this section of the guideline.

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**2014 surveillance summary**

No relevant evidence was identified.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

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**1.20 Review**

**Recommendations in this section of the guideline**

1.20.1 Children, young people and adults with epilepsy should have a regular structured review and be registered with a general medical practice. [2004]
1.20.2 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]

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

1.20.4 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]

1.20.5 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]

1.20.6 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]

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

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

1.20.9 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]

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

1.20.11 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]

2018 surveillance summary
No relevant evidence was identified.

2014 surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The absence of new evidence indicates that there is no need to update this section of the guideline.

No new evidence. Recommendations are unlikely to change.
Research recommendations

Newly diagnosed seizures (focal and generalised) – monotherapy

4.1 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.

Summary of findings

- New evidence relevant to the research recommendation was found (see Focal (aka partial) seizures, newly diagnosed/monotherapy and Pharmacological treatment of newly diagnosed generalised tonic–clonic (GTC) seizures). An update of the related recommendations is planned.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

Epilepsy syndromes

4.2 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?

Summary of findings

- New evidence relevant to the research recommendation was found (see Pharmacological treatment of Dravet syndrome, Lennox-Gastaut syndrome and benign epilepsy with centrotemporal spikes). An update of the related recommendations is planned.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

Infantile spasms

4.3 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?

Summary of findings

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Surveillance decision
This research recommendation will be considered again at the next surveillance point.

Treatment of convulsive status epilepticus (that is, not just refractory)
4.4 What is the most effective and safest AED to treat:
- established (usually lasting longer than 30 minutes) convulsive status epilepticus
- refractory convulsive status epilepticus?

Summary of findings
- New evidence relevant to the research recommendation was found. An update of the related recommendation is planned.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

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

Summary of findings
- New evidence relevant to the research recommendation was found. An update of the related recommendation is planned.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

References


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