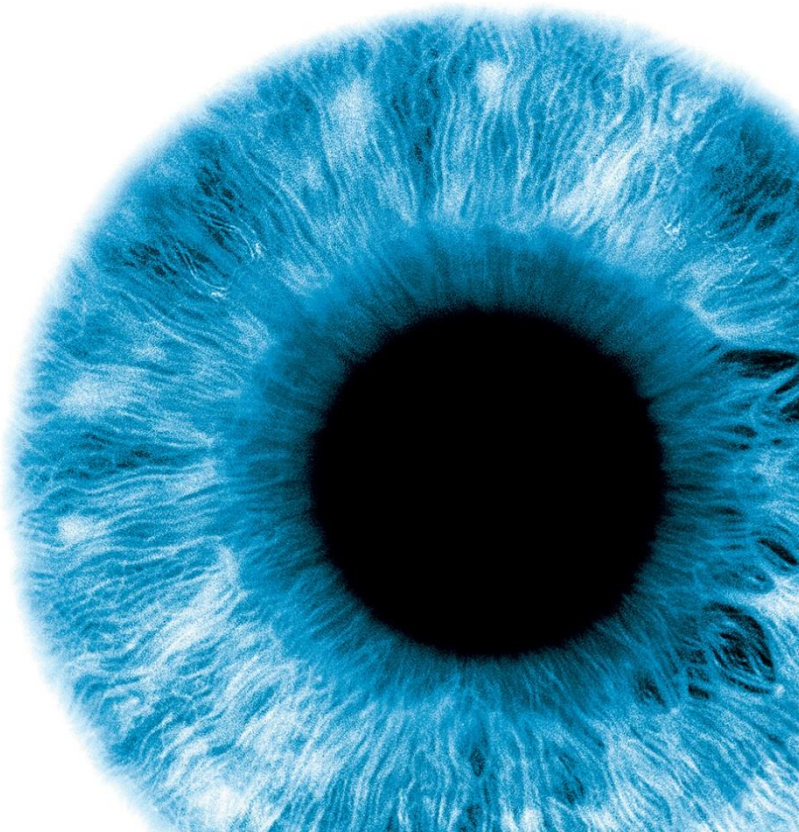
NICE National Institute for Health and Care Excellence

The epilepsies

Evidence Update February 2014

A summary of selected new evidence relevant to NICE clinical guideline 137 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' (2012)

Evidence Update 53



Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NICE Evidence Services topic page for epilepsies.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NICE Evidence Services are a suite of services that provide online access to high quality, authoritative evidence and best practice.

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Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **The epilepsies.** NICE clinical guideline 137 (2012)

A search was conducted for new evidence from 3 June 2010 to 10 September 2013. A total of 8293 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 15 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE products

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE products has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following:

Technology appraisals

[1] Epilepsy (partial) – retigabine (adjuvant). NICE technology appraisal 232

Evidence summaries: new medicines

- Partial-onset seizures in epilepsy: perampanel as adjunctive treatment. Evidence summary: new medicine 7
- Partial-onset seizures in epilepsy: zonisamide as monotherapy. Evidence summary: new medicine 17

NICE Pathways

- Epilepsy. NICE Pathway

Quality standards

- The epilepsies in adults. NICE quality standard 26
- The epilepsies in children and young people. NICE quality standard 27

Other relevant information

- Medicines and Healthcare Products Regulatory Agency. Antiepileptics: changing products. November 2013
- Medicines and Healthcare Products Regulatory Agency. Sodium valproate: special reminder on risk of neurodevelopmental delay in children following maternal use. November 2013

[1] NICE-accredited guidance is denoted by the Accreditation Mark

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Information ***Sudden unexpected death in epilepsy*** • Adults with refractory epilepsy are at lower risk of sudden unexpected death in epilepsy (SUDEP) if they are treated with effective doses of adjunctive anti-epileptic drugs (AEDs).		✓
Investigations ***Neuropsychological assessment*** • Psychiatric comorbidities negatively affect quality of life in people with epilepsy. Early detection and treatment of psychiatric comorbidities may, therefore, be of benefit in all people with epilepsy.		✓
Pharmacological treatment ***Switching between AED products*** • The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued new advice about oral AEDs and switching between different manufacturers' products of a particular drug. The MHRA classifications can help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. ***Perampanel for adjunctive treatment of refractory focal seizures*** • 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. ***Clobazam for adjunctive treatment of Lennox–Gastaut syndrome*** • Limited evidence suggests that clobazam may reduce the incidence of drop seizures and total seizures when used as an adjunctive therapy in people with Lennox–Gastaut syndrome.	✓*	✓ ✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

Key point	Potential impact on guidance: Yes	Potential impact on guidance: No
Referral for complex or refractory epilepsy ***Early surgery for drug-resistant temporal lobe epilepsy*** • Early surgical treatment in patients with epilepsy refractory to treatment with 2 AEDs may offer better seizure control than ongoing drug therapy.		✓
Ketogenic diet ***Modified Atkins diet for refractory childhood epilepsy*** • The modified Atkins diet may be effective at controlling seizures in children with refractory epilepsy.		✓
Prolonged or repeated seizures and convulsive status epilepticus ***Adherence to protocols for managing generalised convulsive status epilepticus*** • Treating patients with generalised convulsive status epilepticus according to a guideline-based protocol improves outcomes. ***Sodium valproate in generalised convulsive status epilepticus*** • Limited evidence suggests that intravenous sodium valproate may be as effective as intravenous phenytoin and have a better safety profile in patients with generalised convulsive status epilepticus.		✓ ✓
Women and girls with epilepsy ***In utero exposure to AEDs and risk of congenital malformations*** • Among women who take AEDs, particularly sodium valproate, during pregnancy, those who have children with congenital abnormalities are at higher risk of having fetal malformations in subsequent pregnancies exposed to AEDs than women whose first pregnancies did not result in fetal malformations. ***In utero exposure to AEDs and cognitive outcome*** • Limited evidence suggests that compared with other AEDs, sodium valproate during pregnancy has a negative, dose-dependent effect on long-term cognitive outcomes in offspring. Periconceptional folic acid may lessen the effect of AED use during pregnancy on the child's intelligence quotient (IQ). ***Breastfeeding*** • Limited evidence suggests that AED use while breastfeeding does not affect cognitive outcome in children exposed to AEDs in utero.		✓ ✓ ✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Principle of decision making

No new key evidence was found for this section.

1.2 Coping with epilepsy

No new key evidence was found for this section.

1.3 Information

Sudden unexpected death in epilepsy

NICE clinical guideline 137 (NICE CG137) advises that the risk of sudden unexpected death in epilepsy (SUDEP) can be minimised by optimising seizure control and being aware of the potential consequences of nocturnal seizures. It recommends that information on SUDEP should be included in literature on epilepsy to show why preventing seizures is important.

A systematic review and meta-analysis by **Ryvlin et al. (2011)** investigated whether receiving effective doses of anti-epileptic drugs (AEDs) reduced the risk of SUDEP in patients with refractory epilepsy. The review included double-blind, randomised controlled trials of adjunctive AEDs in adults with uncontrolled focal or primary generalised tonic–clonic seizures. Patients in these trials were classified into 3 groups according to treatment received: effective doses of AEDs, non-effective doses of AEDs, or placebo. All deaths were classified as possible, probable or definite SUDEP, or another cause. The primary outcome was the incidence of definite and probable SUDEP in patients receiving effective doses of AEDs compared with those on placebo.

In the 112 eligible trials identified, 21,224 patients (5589 patient-years) received 27 AEDs at 86 dose levels, of which 8 dose levels were deemed non-effective. A total of 33 deaths were reported in 19 trials: 20 (reported in 14 trials) were SUDEP (11 definite, 7 probable and 2 possible) and 13 were from other causes (for example, traumatic shock, suicide and cerebral haemorrhage).

Compared with patients allocated to placebo, patients assigned to effective doses of AEDs had:

- A lower incidence of definite and probable SUDEP (odds ratio [OR]=0.17, 95% confidence interval [CI] 0.05 to 0.57, p=0.0046).
- A reduced frequency of all causes of death (OR=0.37, 95% CI 0.17 to 0.81, p=0.0131).

When patients on effective doses and those on non-effective doses of AEDs were pooled, the likelihood of definite and probable SUDEP in patients on any dose of AEDs was lower than in those on placebo (OR=0.14, 95% CI 0.04 to 0.47, p=0.0012).

Limitations of the evidence included that the absolute incidence of SUDEP was low and many of the trials were small and of short duration.

The evidence suggests that adults with refractory epilepsy are at lower risk of SUDEP if they are treated with effective doses of adjunctive AEDs. This evidence is consistent with the advice in NICE CG137 that the risk of SUDEP can be minimised by optimising seizure control.

Key reference

Ryvlin P, Cucherat M, Rheims S (2011) Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurology 10: 961–8

1.4 Following a first seizure

No new key evidence was found for this section.

1.5 Diagnosis

No new key evidence was found for this section.

1.6 Investigations

Neuropsychological assessment

NICE CG137 makes several recommendations relating to psychological comorbidity in people with epilepsy. Children, young people and adults with epilepsy, and their families and/or carers, should be given, and have access to sources of, information about psychological issues. In particular, the physical, psychological and social needs of young people with epilepsy should always be considered by healthcare professionals. Psychiatric and psychological conditions in patients with epilepsy should be managed in accordance with other pieces of NICE guidance.

NICE CG137 suggests that 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. 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.

The guidance also recommends that in people with complex or refractory epilepsy whose seizures are not controlled and/or there is diagnostic uncertainty or treatment failure, referral to tertiary services for further assessment should be considered when psychological and/or psychiatric comorbidity is present.

In addition, NICE CG137 warns that treatment with AEDs is associated with a small risk of suicidal thoughts and behaviour. The evidence available when the guidance was updated in 2012 suggested that this increased risk applies to all AEDs and may be seen as early as 1 week after starting treatment. Healthcare professionals should maintain a high level of vigilance for neuropsychiatric issues that may arise as a result of pharmacological treatment.

NICE has published a number of other relevant guidelines on the management of mental health conditions; for example, the guidance 'Depression with a chronic physical health problem' (CG91).

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 prospective cohort study in the USA by **Baca et al. (2011)** assessed how epilepsy status and psychiatric and other comorbidities affect HRQoL in young people with epilepsy. Children aged 0–15 years diagnosed with epilepsy were recruited between 1993 and 1997 and followed up 9 years later between 2002 and 2006. At follow-up, children were classified as having ever had 1 of 4 chronic comorbidities: a psychiatric disorder; a neurodevelopmental spectrum disorder; migraine; or a chronic medical condition. HRQoL at follow-up was reported by the young people and their parents by using the Child Health Questionnaire (11 scales and 2 global items for child-reported measures; 12 scales, 2 global items and physical and psychosocial summary items for parent-reported measures).

A total of 613 children with epilepsy (mean age at diagnosis 5.1 years) were enrolled in the study and 277 (45.2%) were followed up 9 years later as young people (mean age 13.0 years). 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, 14.8% had migraine and 23.8% had a chronic medical condition. In a multiple linear regression model, having a psychiatric disorder was significantly associated with worse HRQoL across the majority of the quality of life scales – as reported by both the young adults (6 of 11 scales and 1 global item) and by their parents (7 of 12 scales, 1 global item and the psychosocial summary score, $p \leq 0.0125$ for all). Although parent-proxy HRQoL was strongly associated with neurodevelopmental spectrum disorders (6 of 11 scales), child-reported HRQoL was not (2 of 11 scales).

A systematic review by **Taylor et al. (2011)** sought to identify factors that predicted HRQoL and resource use in adults with epilepsy. Studies that evaluated the association between demographic, psychosocial or disease factors and either HRQoL or epilepsy-related costs or resource use were eligible. A total of 107 studies were identified: 93 assessed HRQoL and 16 reported costs or resource use (2 studies evaluated both quality of life and costs). Meta-analysis was not done because of the range of tools used to measure HRQoL and the variability in the measures of association reported in the studies.

Among the studies on HRQoL, 53 used multivariate analysis to assess the predictive value of demographic, psychosocial or disease factors. In the 51 cross-sectional studies, age, gender and marital status were not associated with HRQoL. The evidence on whether education level and employment status affected HRQoL was inconsistent. Depression and anxiety were predictive of poor HRQoL, in both patients with refractory epilepsy and those whose epilepsy was controlled by AEDs, as was the presence of physical or psychological comorbidity. Seizure frequency was negatively associated with HRQoL. However, type of seizure, age at diagnosis and duration of epilepsy did not appear to have an effect on HRQoL, and the evidence on AEDs and drug-related adverse effects was inconclusive. Two prospective studies found that epilepsy surgery improved HRQoL. The 16 studies on predictors of epilepsy-related costs and resource use were of poor quality and of insufficient number to draw any conclusions.

Limitations of the Baca et al. (2011) study included that HRQoL was measured using a generic instrument that may not have been sensitive to epilepsy. Taylor et al. (2011), however, included studies that used epilepsy-specific measures of HRQoL as well as generic tools. In addition, the majority (80.4%) of the parents studied by Baca et al. (2011) were white, so the sample may not reflect the wider population, and a large number of children were lost to follow-up or excluded from the final analysis (55%). Taylor et al. (2011) was limited by the nature of the studies included in the review: most were cross-sectional rather than prospective; many had a relatively small sample size; the methodology of the studies was poor to moderate; and few recruited consecutive patients so were at risk of selection and response bias.

Evidence suggests that psychiatric comorbidities negatively affect quality of life in people with epilepsy. Early detection and treatment of psychiatric comorbidities may, therefore, be of benefit in all people with epilepsy. The evidence is consistent with the advice in NICE CG137 that people with epilepsy, and their families and/or carers, should be given, and have access to sources of, information about psychological issues.

Although the need to investigate psychiatric comorbidity in people with epilepsy appears to be important, how this is best managed may be less certain. The International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy offer some advice on how to manage psychiatric comorbidity in people with epilepsy. Further studies may however be needed to investigate the effectiveness of interventions for psychiatric comorbidities in this population. In addition, health economic analysis studies are required to determine predictors of cost and resource use.

Key references

Baca CB, Vickrey BG, Caplan R et al. (2011) Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 128: e1532–e1543 [NIH Public Access author manuscript – full text]

Taylor RS, Sander JW, Taylor RJ et al. (2011) Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia 52: 2168–80

Supporting reference

Kerr MP, Mensah S, Besag F et al. (2011) International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia 52: 2133–2138

1.7 Classification

No new key evidence was found for this section.

1.8 Management

No new key evidence was found for this section.

1.9 Pharmacological treatment

Switching between AED products

NICE CG137 notes that different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles. The guideline therefore recommends consistent supply of a particular manufacturer's AED preparation, unless the prescriber, in consultation with the patient, considers that this is not a concern.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued new advice about oral AEDs and switching between different manufacturers' products of a particular drug. This includes switching between branded original and generic products, and between different generic products of a particular drug. The MHRA notes that different AEDs vary considerably in their characteristics, which influences the risk of whether switching between different products may cause adverse effects or loss of seizure control. Following a review of the available evidence, the MHRA's Commission on Human Medicines has classified AEDs into 3 categories:

- **Category 1** – phenytoin, carbamazepine, phenobarbital and primidone
  For these drugs, doctors are advised to ensure that the patient is maintained on a specific manufacturer's product.

- **Category 2** – valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide and topiramate
  For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history.
- **Category 3** – levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide and vigabatrin
  For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns, such as patient anxiety or risk of confusion or dosing errors.

A cross reference to this advice has been added to NICE CG137. A NICE Medicines Evidence Commentary is available to contextualise the changes to the guideline.

The MHRA classifications can help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. The agency's advice has been incorporated into NICE CG137 as a footnote. The evidence is, therefore, consistent with the recommendations in NICE CG137. The EUAG members emphasised the importance of reporting adverse events resulting from switching AEDs to the MHRA's Yellow Card Scheme to support the evidence base for future MHRA decisions.

Perampanel for adjunctive treatment of refractory focal seizures

Perampanel is a selective, non-competitive antagonist of the AMPA glutamate receptor. It is licensed for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in people with epilepsy aged 12 years and older (the term 'focal' has been used instead of 'partial onset' in NICE CG137). The drug is not discussed in NICE CG137 because it was not available in the UK at the time the guidance was published. Perampanel was considered not appropriate for a NICE technology appraisal.

NICE Evidence summary: new medicine 7 'Partial-onset seizures in epilepsy: perampanel as adjunctive treatment' reviewed the 3 pieces of evidence on perampanel that were identified for this Evidence Update (see the key references **French et al. [2012]**, **French et al. [2013]** and **Krauss et al. [2013]** below)[2].

The evidence suggests 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. Perampanel was not included in NICE CG137; the evidence may, therefore, have a potential impact on the guideline, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Key references

French JA, Krauss GL, Biton V et al. (2012) Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 79: 589–96 [NIH Public Access author manuscript – full text]

French JA, Krauss GL, Steinhoff BJ et al. (2013) Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. Epilepsia 54: 117–25

Krauss GL, Serratosa JM, Villanueva V et al. (2012) Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 78: 1408–15

[2] Evidence Updates do not provide commentary on evidence already analysed by a NICE Evidence summary: new medicine.

Clobazam for adjunctive treatment of Lennox–Gastaut syndrome

NICE CG137 recommends that children with suspected Lennox–Gastaut syndrome should be discussed with, or referred to, a tertiary paediatric epilepsy specialist as part of the initial assessment. Sodium valproate should be offered as first-line treatment, with lamotrigine, rufinamide and topiramate recommended as adjunctive treatment. Clobazam is a benzodiazepine licensed for the adjunctive treatment of epilepsy. It is not specifically licensed for the adjunctive treatment of Lennox–Gastaut syndrome and is not discussed in NICE CG137 in relation to this use.

A randomised controlled trial by **Ng et al. (2011)** evaluated the efficacy and safety of clobazam as adjunctive therapy in people with Lennox–Gastaut syndrome. Patients aged 2–60 years who had developed Lennox–Gastaut syndrome before they were 11 years and who were taking at least 1 AED (except a benzodiazepine, other than for rescue therapy) were recruited from 51 sites in the USA, India, Europe and Australia. Patients were stratified by weight and randomly assigned to 1 of 4 groups: placebo; low-dose clobazam (target dose 0.25 mg/kg/day, maximum dose 10 mg/day); medium-dose clobazam (target dose 0.5 mg/kg/day, maximum dose 20 mg/day); or high-dose clobazam (target dose 1.0 mg/kg/day, maximum dose 40 mg/day). Clobazam was administered as 5 mg tablets. Allocation was concealed. The study comprised a 4-week baseline period, 3 weeks of titration and a 12-week maintenance period, followed by either an open label study or a taper period of 2 or 3 weeks. The primary outcome was decrease in the average weekly frequency of drop seizures compared with baseline, as recorded by patients' parents or caregivers.

A total of 238 patients enrolled in the trial (mean age 12.4 years, range 2–54 years; 22% over 16 years), and 177 (74.4%) completed the study. The modified intention to treat (mITT) population used for the efficacy analysis comprised all randomised patients who had baseline data, received at least 1 dose of study drug and had at least 1 daily seizure measurement recorded during the maintenance period (n=217). In this analysis, the mean reduction from baseline in average weekly rate of drop seizures, and all seizures (drop and non-drop), was significantly greater with all the clobazam doses than with placebo:

- Placebo: drop seizures=12.1%; all seizures=9.3%.
- Low dose: drop seizures=41.2% (p=0.0120); all seizures=34.8% (p=0.0414).
- Medium dose: drop seizures=49.4% (p=0.0015); all seizures=45.3% (p=0.0044).
- High dose: drop seizures=68.3% (p<0.0001); all seizures=65.3% (p<0.0001).

Average weekly rates of non-drop seizures increased from baseline by 76.3% in the placebo group, 53.3% in the low-dose group and 3.3% in the medium-dose group, and decreased by 40.0% in the high-dose group. However, these differences were not significantly different.

The proportion of patients with a 50% or greater reduction in average weekly rate of drop seizures (response rate) was:

- Placebo: 31.6% (18/57).
- Low dose: 43.4% (23/53).
- Medium dose: 58.6% (34/58).
- High dose: 77.6% (38/49).

The response rate was significantly different from placebo for the medium-dose (p=0.0159) and high-dose groups (p<0.0001), but not for the low-dose group (p=0.3383).

In the safety population (all randomised patients who received at least 1 dose of study drug, n=238), similar proportions of patients receiving clobazam and placebo had at least 1 adverse event (low-dose group=72.4%, medium-dose group=88.7%, high-dose group=76.3%, placebo group=67.8%).

Limitations of the evidence included that:

- The study was small (49–58 patients per study group) and of short duration (patients were monitored for only 15 weeks once they had received the study drug).
- Although the report specified that approximately 50% of participants were also receiving valproic acid, valproate semisodium or valproate sodium, it does not give full details of which other medications participants were taking.

Limited evidence suggests that clobazam may reduce the incidence of drop seizures and total seizures when used as an adjunctive therapy in people with Lennox–Gastaut syndrome. Given the limitations of the study, the evidence is unlikely to have an impact on NICE CG137. Further, larger studies with longer term follow-up are needed to determine the efficacy and safety of clobazam in patients with Lennox–Gastaut syndrome.

Key reference

Ng YT, Conry JA, Drummond R et al. (2011) Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 77: 1473–81

1.10 Referral for complex or refractory epilepsy

Early surgery for drug-resistant temporal lobe epilepsy

NICE CG137 recommends that children, young people and adults whose seizures are not controlled or in whom treatment fails should be referred to tertiary services soon for further assessment. Referral should be considered when 1 or more of the following criteria are present:

- the epilepsy is not controlled with medication within 2 years
- management is unsuccessful after 2 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 comorbidity
- there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome.

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

The NICE quality standard 'The epilepsies in adults' (NICE QS26) also emphasises the need for early referral:

- Quality statement 7: Adults who meet the criteria for referral to a tertiary care specialist are seen within 4 weeks of referral (which may include assessment for surgery).

A US-based randomised, controlled, parallel-group trial by **Engel et al. (2012)** investigated whether surgery soon after 2 AEDs have been found not to control epilepsy is better at reducing seizure frequency than continued medical management. The Early Randomised Surgical Epilepsy Trial identified patients with mesial temporal lobe epilepsy who had experienced disabling seizures for no more than 2 years and had tried 2 branded AEDs. Participants were randomly assigned to receive surgery (anteromesial temporal resection) and drug treatment or drug treatment alone, and were followed up every 3 months for 24 months. Drug treatment could include multiple AEDs and was monitored by an independent panel of clinical pharmacologists who were blind to study group assignment. The primary outcome was freedom from disabling seizures during the second year of follow-up.

Across the 16 study centres, 38 patients were randomised after presurgical evaluation: 15 to the surgery group (14 of whom received surgery) and 23 to the drug-treatment group (16 of whom received drug treatment only and 7 of whom received surgery). Allocation was concealed. In an intention-to-treat analysis, patients in the surgery group were significantly more likely than those in the drug-treatment group to be free from seizures during the second year of the study (73% versus 0%, OR=∞, 95% CI 11.8 to ∞, p<0.001). Patients in the surgery group also had a greater increase in HRQoL than those in the drug-treatment group at 6, 12 and 18 months (p<0.009), although the difference was not significant at 2 years.

Limitations of the evidence included that:

- A sample size of 200 participants was planned, but only 76 potential patients were identified during 2 years of recruitment (38 of whom were randomised).
- The 2 treatment groups differed in mean age and sex at baseline. Mean age among patients in the surgery group was 6.6 years greater than in the drug-treatment group, and only one-quarter (26.7%) of patients in the surgery group were male, compared with nearly two-thirds (60.9%) of patients in the drug-treatment group.
- Nearly one-third (7/23, 30%) of the drug-treatment group received surgery.
- Neither the trial investigators nor the participants were blinded to treatment received.
- The study had strict inclusion criteria and was performed at level 4 epilepsy centres, which provide the highest level of epilepsy care in the US (such as complex forms of intensive neurodiagnostics monitoring). The results may not, therefore, be generalisable to patients with temporal lobe epilepsy who do not meet the inclusion criteria or who do not have surgery at similar-level epilepsy centres.

The evidence suggests that early surgical treatment in patients with epilepsy refractory to treatment with 2 AEDs may offer better seizure control than ongoing drug therapy. This evidence is consistent with the recommendation in NICE CG137 that patients whose epilepsy is not controlled with medication within 2 years or after trying 2 drugs should be assessed for epilepsy surgery.

Key reference

Engel J, McDermott MP, Wiebe S et al. (2012) Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 307: 922–30

1.11 Psychological interventions

No new key evidence was found for this section.

1.12 Ketogenic diet

Modified Atkins diet for refractory childhood epilepsy

NICE CG137 recommends that children and young people with epilepsy whose seizures have not responded to appropriate AEDs should be referred to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet (a specific diet that is high in fat but low in carbohydrates and protein). The guidance does not make any recommendations on other dietary methods of controlling seizures, such as the modified Atkins diet (also known as the modified ketogenic diet).

A randomised controlled trial in India by **Sharma et al. (2013)** investigated the efficacy of the modified Atkins diet in children with refractory epilepsy. The study enrolled from a single centre children aged 2–14 years (n=102; 78 boys) who had daily seizures, or more than 7 seizures a week, despite the use of at least 3 AEDs. Children were randomised to the modified Atkins diet (n=50; carbohydrate 10 g/day, no protein restriction, intake of fat actively encouraged) or normal diet (n=52) for 3 months. Allocation was concealed. AEDs were not

changed during the study period unless medically indicated. The study period was preceded by a 4-week baseline period in which daily seizures were recorded by the participants' parents. The primary outcome measure was the average number of seizures per week at 3 months compared with baseline.

The mean seizure frequency (as a percentage of baseline) among patients on the modified Atkins diet was 59% (95% CI 44 to 75%), compared with 96% in the control group (95% CI 82 to 109%, p=0.003). A greater proportion of children on the modified Atkins diet than on the control diet had more than 50% seizure reduction or more than 90% seizure reduction (p<0.001 and p=0.005, respectively). The modified Atkins diet was generally well tolerated: 46% of children experienced constipation, the most common of 6 side effects reported.

Limitations of the evidence included that:

- 44% of the children on the modified Atkins diet were vegetarian, which may not be mirrored in UK children.
- 77% of participants were male, which may limit the generalisability of these findings.
- The study was not blinded and relied on reporting by parents for the primary outcome of seizure frequency.

The evidence suggests that the modified Atkins diet may be effective at controlling seizures in children with refractory epilepsy. Although the evidence suggests that the modified Atkins diet may be effective, limitations of the study mean that this evidence does not have an impact on NICE CG137.

Further studies are needed to replicate these findings in a European setting. The EUAG recommended that additional research might benefit from including assessment for a possible glucose transporter defect (for example, cerebrospinal fluid to plasma glucose ratio, or mutation analysis of the *SLC2A1* gene), for which ketogenic diet (including the modified Atkins diet) would be the treatment of choice.

Key reference

Sharma S, Sankhyan N, Gulati S et al. (2013) Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia 54: 481–6

1.13 Vagus nerve stimulation

No new key evidence was found for this section.

1.14 Prolonged or repeated seizures and convulsive status epilepticus

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

NICE CG137 recommends that children, young people and adults who have prolonged (lasting 5 minutes or more) or repeated (3 or more in an hour) convulsive seizures in the community should be given immediate emergency care and treatment. Buccal midazolam is recommended as first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Rectal diazepam may be administered if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, intravenous lorazepam should be administered.

The guidance also recommends that children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus) who are in hospital should be given intravenous lorazepam as first-line treatment. If intravenous lorazepam is unavailable, then intravenous diazepem should be administered, or buccal midazolam if immediate

intravenous access cannot be secured immediately. If seizures continue, intravenous phenobarbital or phenytoin should be administered as second-line treatment.

An appendix of the guideline sets out detailed protocols for treating convulsive status epilepticus in adults and children.

Adherence to protocols for managing generalised convulsive status epilepticus

A cohort study in France by **Aranda et al. (2010)** evaluated whether adherence to an established management protocol improved outcomes in people with generalised convulsive status epilepticus. The study prospectively enrolled all patients aged 18 years or older who presented with status epilepticus over a 16 month period in the Haute-Garonne district of France. The protocol used was derived from French, European and US guidelines on the management of status epilepticus (but differed from protocols currently recommended by NICE CG137) and comprised:

- First-line treatment (both in and out of hospital): diazepam or clonazepam with fosphenytoin during the first 20 minutes of the episode.
- Second-line treatment:
  - in hospital: phenobarbital, sodium valproate or levetiracetam
  - out of hospital: phenobarbital, propofol or midazolam.
- Third-line treatment (in hospitalised patients whose episode lasted 90 minutes or longer): phenobarbital, propofol or midazolam.

The physician who enrolled the patient recorded data on management at the time of the episode or within the 7 days after the episode started. The primary outcome was seizure termination, defined as termination of seizure activity within 20 minutes of AED initiation, with no recurrence within 1 hour and no need for further AEDs to stop the episode.

There were 101 episodes of generalised convulsive status epilepticus, and intravenous AEDS were administered as initial treatment in 100 of these episodes. Among these 100 patient episodes, one-third (38%) received first-line treatment with the drugs and doses set out in the protocol. Patients whose first-line treatment was per protocol were significantly more likely to have seizure termination than those whose treatment did not adhere to the protocol (74% versus 29%, univariate OR=7.7, 95% CI 3.1 to 19.3, p<0.0001). Patients who had seizure termination with first-line treatment also spent less time in intensive care (median stay=1 day, 95% CI 1 to 2 days, compared with 2 days, 95% CI 1 to 5.5 days, p<0.0001) and less time in hospital overall (median stay=3 days, 95% CI 2 to 11 days, compared with 7 days, 95% CI 3 to 18 days, p=0.009). Adherence to protocol was 74% in the 54 patients who received second-line treatment. Patients whose second-line treatment was per protocol were significantly more likely to have seizure termination than those whose treatment did not adhere to the protocol (83% versus 50%, OR=4.7, 95% CI 1.3 to 17.8, p=0.02).

One limitation of the study is that emergency services in France differ considerably from those in the UK. The French ambulance system includes doctor-led medical emergency teams, which allow complete medical management in out-of-hospital settings, whereas ambulances in the UK have paramedics only. Another limitation of this study is that it was not randomised or blinded, and the management protocol was different from that recommended by NICE CG137.

The evidence suggests that treating patients with generalised convulsive status epilepticus according to a guideline-based protocol improves outcomes, and is consistent with the inclusion in NICE CG137 of a recommended protocol for managing status epilepticus.

Key reference

Aranda A, Foucart G, Ducassé JL et al. (2010) Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia 51: 2159–67

Sodium valproate in generalised convulsive status epilepticus

A systematic review by **Brigo et al. (2012)** explored the efficacy and safety of intravenous sodium valproate in patients with generalised convulsive status epilepticus[3]. Randomised controlled trials were included of intravenous sodium valproate compared with another AED, placebo or no treatment in patients of any age with status epilepticus. Five studies in India, Israel and China that compared intravenous sodium valproate with either intravenous phenytoin or intravenous diazepam in hospitalised patients were identified. Only the 3 studies comparing intravenous sodium valproate with intravenous phenytoin (n=152) had enough data for meta-analysis.

No significant difference was observed between intravenous sodium valproate and intravenous phenytoin for seizure freedom at 24 hours (84.9% versus 90.9% of patients, relative risk [RR]=0.96, 95% CI 0.88 to 1.06, p=0.46; 3 studies, n=152). There was also no difference between intravenous sodium valproate and intravenous phenytoin for seizure cessation within 30 minutes of drug administration (67.9% versus 50.0%, RR=1.31, 95% CI 0.93 to 1.84, p=0.13; 2 studies, n=95). Patients on intravenous sodium valproate were less likely to experience adverse effects than those on intravenous phenytoin (9.8% versus 34.8%, RR=0.31, 95% CI 0.12 to 0.85, p=0.02; 2 studies, n=64).

Limitations of the study included that:

- The numbers of studies and patients included in the analysis were small.
- All studies included in the review had a high or unclear risk of publication bias because they did not use adequate methods to conceal randomisation.
- Among the 3 studies comparing intravenous sodium valproate with intravenous phenytoin, 1 gave sodium valproate only after initial benzodiazepine was ineffective rather than as first-line treatment.

Limited evidence suggests that intravenous sodium valproate may be as effective as intravenous phenytoin and have a better safety profile in patients with generalised convulsive status epilepticus. The EUAG agreed that a safer alternative to phenytoin is needed for management of status epilepticus, but the limitations of this evidence prevent definitive assessment of sodium valproate for this indication. As such, the findings are unlikely to have an impact on NICE CG137.

In line with the NICE research recommendation ('What is the most effective and safest AED to treat established convulsive status epilepticus?'), multicentre randomised controlled trials are needed to determine the optimum treatment for convulsive status epilepticus – for example, to compare intravenous levetiracetam, sodium valproate and phenytoin as first-line treatment.

Key reference

Brigo F, Storti M, Del Felice A et al. (2012) IV Valproate in generalized convulsive status epilepticus: a systematic review. European Journal of Neurology 19: 1180–91

1.15 Women and girls with epilepsy

Information and advice for women and girls with epilepsy

NICE CG137 recommends discussing 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. Specifically, the risk of continued use of

[3] Intravenous sodium valproate is licensed for treating people with epilepsy who would normally be maintained on oral sodium valproate and for whom oral therapy is temporarily not possible. It is not included in NICE CG137 as a treatment for status epilepticus.

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, should be discussed.

The MHRA has issued a special reminder on the risk of neurodevelopmental delay in children following maternal use of sodium valproate. The agency states that sodium valproate should not be used during pregnancy and in women of childbearing potential unless there is no effective alternative. Women of childbearing potential should not start treatment with sodium valproate without specialist neurological or psychiatric advice, as appropriate depending on the indication. Adequate counselling should be made available to all women of childbearing potential to weigh the risk of teratogenic and neurodevelopmental effects against the benefits of treatment.

The risks and benefits of treatment with individual drugs should be assessed. Limited data are available on risks to the unborn child associated with newer drugs. Healthcare professionals should be aware of the latest data on the risks to the unborn child associated with AED therapy when prescribing for women and girls of present and future childbearing potential. 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, which prospectively collects clinical data from pregnant women with epilepsy who are on 1 or more AEDs.

In utero exposure to AEDs and risk of congenital malformations

Two registry studies, 1 using data from Australia and the other from the UK, provide evidence on the risk of women taking AEDs, who have had 1 birth with congenital abnormalities, having malformations in subsequent offspring.

Vajda et al. (2013) analysed data collected by the Australian Register of Antiepileptic Drugs in Pregnancy between 1999 and 2010. The registry prospectively and retrospectively collected information on pregnant women who took AEDs throughout pregnancy, either for epilepsy or disorders other than epilepsy, and on women with epilepsy who did not take AEDs at least in the first trimester of pregnancy. Information from the end of the first postnatal month and the first postnatal year was used to determine the presence of fetal abnormalities. The first pregnancy enrolled by a woman on the register was considered to be the 'index' pregnancy (even among those women who had previously had pregnancies).

Data on the index pregnancy were available for 1243 women enrolling on the register (all but 37 of whom had epilepsy). For 647 of these women, the index pregnancy was their first pregnancy. The remaining 596 women reported having already had at least 1 pregnancy before enrolling. After enrolment, 228 women went on to have a second pregnancy – 45 of whom subsequently had further pregnancies. Overall, a total of 2637 pregnancies were recorded, 1114 of which took place before the index pregnancy.

In the index pregnancies, women who took sodium valproate during the first trimester of pregnancy (n=337) were more likely than those took other AEDs (n=789) to have a pregnancy with congenital abnormalities (13.1% versus 4.4%, OR 3.24, 95% CI 2.03 to 5.15). The rate of abnormalities in pregnancies exposed to AEDs other than sodium valproate was not appreciably different from the rate when no AEDs were involved (4.4% versus 4.3%). Women whose index pregnancy had resulted in an AED-related fetal abnormality were significantly more likely to have a fetal malformation in their next pregnancy than were women whose index pregnancy was normal despite AED treatment (35.7% versus 3.1%, OR=17.6, 95% CI 4.5 to 68.7). This higher rate of fetal malformations was not significant in the subgroup of women taking AEDs other than sodium valproate during each pregnancy (14.3% versus 1.96%, OR=8.33, 95% CI 0.75 to 92.4) but was significant in those on sodium valproate (57.1% versus 7.0%, OR=17.8, 95% CI 2.7 to 119.1).

Spontaneous or induced abortions had occurred in 264 (44.3%) of the pre-index pregnancies in women who had been pregnant at least once before enrolment. In the remaining 332 pregnancies, congenital abnormalities had occurred in 4 (2.8%) of the 145 pregnancies not exposed to AEDs, 12 (10.1%) of the 119 pregnancies exposed to AEDs other than sodium valproate (OR versus unexposed pregnancies 3.95, 95% CI 1.24 to 12.6) and 11 (16.2%) of the 68 pregnancies exposed to sodium valproate (OR versus unexposed pregnancies 6.80, 95% CI 2.08 to 22.2). However, the difference in rates between pregnancies exposed to sodium valproate and those exposed to AEDs other than sodium valproate was not significant (OR 1.72, 95% CI 0.71 to 4.14).

Campbell et al. (2013) analysed data from the UK Epilepsy and Pregnancy Register. Outcomes were reviewed for women registered between 1996 and 2011 who had 2 or more pregnancies that resulted in a live birth, or a pregnancy loss that had a congenital malformation. The primary outcome was the risk of major or minor congenital malformations. The analysis comprised 1371 singleton pregnancies in 646 women.

In total 83 (12.8%) women had a congenital abnormality in their first pregnancy, 14 of whom had at least 1 more child with a congenital abnormality (recurrence rate=16.9%). Among the 563 women who did not have a congenital abnormality in their first pregnancy, 55 (9.8%) subsequently had a child with a congenital abnormality. Women whose first child had a congenital abnormality were more likely to have a congenital abnormality in a subsequent pregnancy than women whose first child was not malformed (RR=1.73, 95% CI 1.01 to 2.96, p=0.04). The recurrence rates by AED type did not differ significantly, but this finding may have been because the numbers of pregnancies exposed to each AED were small.

Limitations of Vajda et al. (2013) included that the data on previous pregnancies were self-reported by the women in the study; therefore, the retrospective information may be less reliable than the prospective information. Campbell et al. (2013) also used self-reporting to collect data, as well as reporting by healthcare professionals. Both studies were observational, so residual confounding by baseline characteristics is possible. Campbell et al. (2013) had a short period after birth in which fetal malformations could be identified (up to 6 weeks) and was limited by the small number of events.

The evidence suggests that among women who take AEDs, particularly sodium valproate, during pregnancy, those who have children with congenital abnormalities are at higher risk of having fetal malformations in subsequent pregnancies exposed to AEDs than women whose first pregnancies did not result in fetal malformations. The risk of recurrent abnormalities highlighted in this evidence is consistent with the recommendations in NICE CG137 that sodium valproate is associated with a particularly high risk to the unborn child.

Key references

Campbell E, Devenney E, Morrow J et al. (2013) Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. Epilepsia 54: 165–71

Vajda FJ, O'Brien TJ, Lander CM et al. (2013) Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. Epilepsia 54: 181–6

In utero exposure to AEDs and cognitive outcome

An observational, single-blind study at 25 centres in the UK and the USA by **Meador et al. (2013)** assessed the effects of AED use during pregnancy on cognitive outcomes in children. This paper reports findings from the Neurodevelopmental Effects of Antiepileptic Drugs study of pregnant women with epilepsy on AED monotherapy (carbamazepine, lamotrigine, phenytoin or sodium valproate). Assessors blinded to treatment evaluated the cognitive development of these women's offspring at 2, 3, 4.5 and 6 years.

The primary analysis included 311 live births in 305 mothers. Cognitive outcomes were available from at least 1 of the 4 test ages for 279 (90%) children; 224 children completed

6 years of follow-up. Analysis was adjusted for maternal intelligence quotient (IQ), AED type, AED standardised dose, gestational age at birth and use of periconceptional folate. Children exposed to sodium valproate in utero had significantly lower IQ scores at 6 years (mean IQ=97, 95% CI 94 to 101) than those exposed to carbamazepine (mean IQ=105, 95% CI 102 to 108, p=0.0015), phenytoin (mean IQ=108, 95% CI 104 to 112, p=0.0006) or lamotrigine (mean IQ=108, 95% CI 105 to 110, p=0.0003). The negative effect of sodium valproate on IQ worsened with increasing dose (r=−0.56, p<0.001), and was most marked on verbal functioning and memory. IQ at 6 years was higher in children whose mothers used periconceptional folic acid (mean IQ=108, 95% CI 106 to 111) than in those whose mothers did not take folic acid (mean IQ=101, 95% CI 98 to 104, p=0.0009).

Limitations of the evidence included that the sample was relatively small (n=311), a large proportion of participants was lost to 6-year follow-up (28%), no unexposed controls were included and the maternal folic acid data was established retrospectively by self-report.

Limited evidence suggests that compared with other AEDs, sodium valproate during pregnancy has a negative, dose-dependent effect on long-term cognitive outcomes in offspring. Periconceptional folic acid may lessen the effect of AED use during pregnancy on the child's IQ. The evidence is consistent with the recommendation in NICE CG137 that sodium valproate, particularly doses of more than 800 mg/day, is associated with a greater risk to the unborn child. The evidence is also consistent with the recommendation that all women and girls on AEDs should be offered 5 mg/day of folic acid before any possibility of pregnancy. Registry studies give limited information, so further research is needed to confirm these findings and data on more AEDs are required.

Key reference

Meador KJ, Baker GA, Browning N et al. (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 12: 244–52 [NIH Public Access author manuscript – full text]

Breastfeeding

NICE CG137 recommends that all women and girls with epilepsy should be encouraged to breastfeed, except in very rare circumstances. Breastfeeding is generally safe for most women and girls taking AEDs and should be encouraged. However, each mother needs to be supported in the choice of feeding method that bests suits her and her family. The guidance recommends that prescribers should consult individual drug advice in the summary of product characteristics and the British national formulary 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.

A second paper using data from the Neurodevelopmental Effects of Antiepileptic Drugs study by **Meador et al. (2010)** investigated the effects of breastfeeding during AED therapy on the cognitive outcomes of offspring. The study enrolled pregnant women with epilepsy in the UK and USA who were taking AED monotherapy (carbamazepine, lamotrigine, phenytoin or sodium valproate) during pregnancy. Participants were followed up by telephone at 3 months after delivery to check whether they were breastfeeding. Assessors blinded to AED evaluated cognitive outcomes in offspring at 36–45 months old using the Differential Ability Scales.

The primary analysis comprised 194 women and 199 children (5 sets of twins) for whom data on breastfeeding and cognitive outcome at 3 years were available. Overall, 84 (42%) children were breastfed for a median of 6 months (range 3–24 months). The mean adjusted IQ score at 3 years was 99 (95% CI 96 to 103) in all breastfed children and 98 (95% CI 95 to 101) in children who were not breastfed (p=0.49). Maternal IQ was the variable most strongly associated with child IQ (p=0.0001), followed by gestational age (p=0.005), maternal age and

folic acid use around conception (p=0.01 for both). AED type had a weaker association (p=0.04), but AED dose was not associated with child IQ (p=0.05)

This study is limited by the lack of any data on the amount of breastfeeding. In addition, the study had a relatively small sample size (n=199 children), was not randomised and did not include children who were not exposed to AEDs during pregnancy but subsequently exposed during breastfeeding. The study was powered to detect a 0.5 standard deviation effect on IQ in the combined analysis of all AEDs (a clinically meaningful difference) but not for analysis of individual AEDs, so was not able to determine the effects of particular AEDs on IQ.

Limited evidence suggests that AED use while breastfeeding does not affect cognitive outcome in children exposed to AEDs in utero. This finding is consistent with the advice in NICE CG137 that breastfeeding is generally safe for most women and girls taking AEDs and should be encouraged.

Key reference

Meador KJ, Baker GA, Browning N et al. (2010) Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology 75: 1954–60

1.16 Children, young people and adults with learning disabilities

No new key evidence was found for this section.

1.17 Young people with epilepsy

No new key evidence was found for this section.

1.18 Older people with epilepsy

No new key evidence was found for this section.

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

No new key evidence was found for this section.

1.20 Review

No new key evidence was found for this section.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Investigations

- Psychological treatments for psychiatric disorders in people with epilepsy

Pharmacological treatment

- Strategies for improving adherence to antiepileptic drug treatment in patients with epilepsy

Prolonged or repeated seizures and convulsive status epilepticus

- Intravenous valproate for status epilepticus

Further evidence uncertainties for epilepsy can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- The epilepsies. NICE clinical guideline 137 (2012)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 3 June 2010 (the end of the search period of NICE clinical guideline 137) to 10 September 2013 (24 July 2009 to 9 September 2013 for economic evaluations):

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

Table 1 provides details of the MEDLINE search strategy used (based on the search strategy for the reference guidance), which was adapted to search the other databases listed above. The sifting criteria listed below were introduced to help to identify the studies of highest potential relevance, quality and impact:

- Randomised controlled trials and observational studies: minimum sample size of 100 in adults (aged 18 and over) and 30 in children and young people.
- Observational studies: limited to cohort studies only, and those from resource poor countries (defined as those not listed as OECD high income members) were be excluded.
- Economic evaluations: restricted to economic evaluations based on UK or Western European data.

The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews and observational studies, and the National Clinical Guideline Centre filter for quality of life studies.

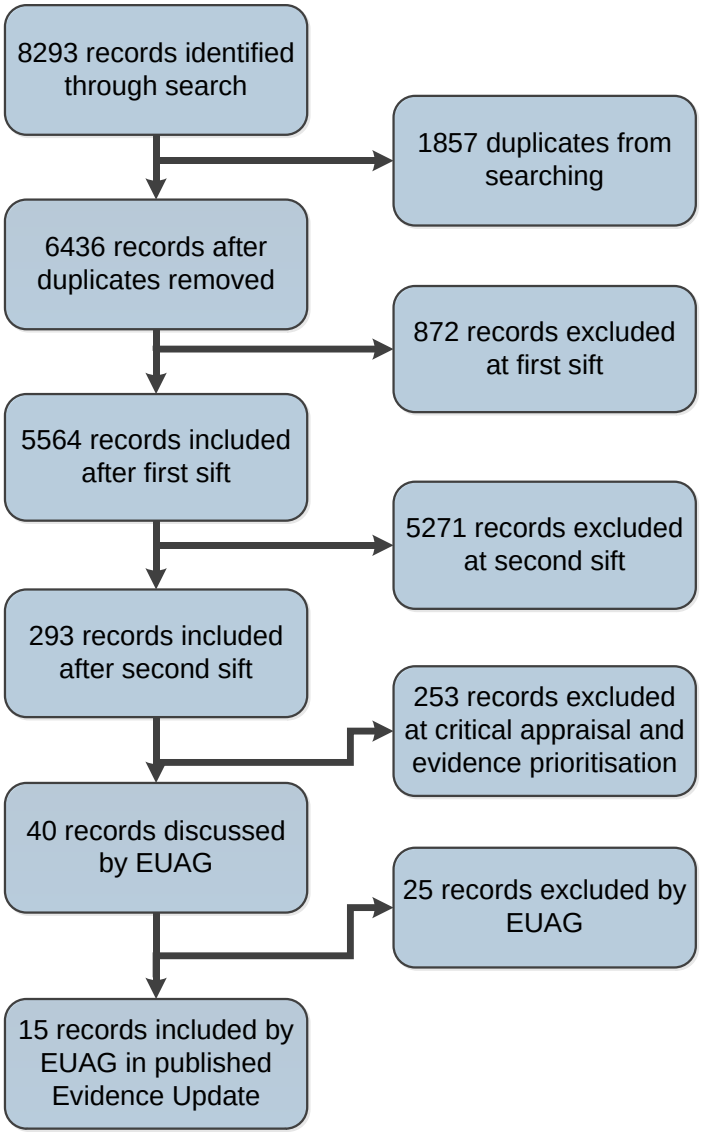
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NICE Evidence Services website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Epilepsy/
2	(epilep$ or continuous spike wave of slow sleep or landau-kleffner syndrome or lennox-gastaut syndrome or Dravet syndrome or Panayiotopolous syndrome or infant$ spasm$).ti,ab.
3	(seizure$ or convulsion$).ti,ab.
4	or/1-3

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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