Healthcare Improvement Scotland

SIGN

SIGN 143 • Diagnosis and management of epilepsy in adults

A national clinical guideline

May 2015 · Revised 2018

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network

Diagnosis and management of epilepsy in adults

A national clinical guideline

Revised 2018

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Since the publication of SIGN 70 in 2003 there has been an expansion in the number of epilepsy specialists, and improved and faster access to clinics devoted to epilepsy and first seizures. The number of drugs available to treat epilepsy has increased and the range of imaging, surgical and interventional techniques has risen. Collectively, these changes have helped to bring about the improvements in care highlighted as necessary in the previous guideline.

Despite these improvements, however, the scale and scope of the need for a guideline should not be underestimated. In Scotland there are 54,000 people with active epilepsy affecting all ages,[1, 2] and there will be between 2,000 and 3,500 new diagnoses each year.[1] The low number of epilepsy specialists in previous decades means that many people with epilepsy across the UK have been diagnosed and treated by non-specialists in both primary and secondary care. Up to a quarter of patients referred for specialist management of apparent drug-resistant epilepsy do not have epilepsy and around 50% of referrals to first seizure clinics result from events which are not epileptic. There is evidence that management can sometimes be suboptimal,[3-5] and with some intervention, readily improved.[3, 5] Epilepsy carries a small but significant risk of mortality which is increased where seizure control is incomplete. Specific concerns surround initial diagnosis, drug treatment, management of pregnant women with epilepsy and the provision of patient information. It is likely that the incidence of sudden unexpected death in epilepsy (SUDEP) could be reduced if antiepileptic treatment was always optimised and patients made aware of the importance of adherence. There is room for improvement in the diagnosis and management of *status epilepticus* and in the care and advice provided for women of reproductive age. People with epilepsy often report inadequate provision of information and advice. Such needs were highlighted in the previous guideline and, over ten years on, there remains scope for the development of better epilepsy services in both primary and secondary care.

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 70: Diagnosis and management of epilepsy in adults to reflect the most recent evidence.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 70. The original supporting evidence was not reappraised by the current guideline development group.

1.1.2 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

In September 2018, this guideline was updated to take account of new drug safety advice from the Medicines and Healthcare products Regulatory Agency (MHRA), published in April 2018, relating to use of valproate medicines in women and girls of childbearing potential.[454] Warnings have been inserted where relevant in sections 4 and 5 to reflect this advice.

2	Key recommendations	New
3	Diagnosis	Updated
4	Treatment	Updated September 2018
5	Epilepsy and women's health	Updated September 2018
6	Psychiatric comorbidity	New
7	Sleep	New
8	Mortality	New
9	Models of care	Completely revised
10	Provision of information	Completely revised
11	Implementing the guideline	Completely revised
12	The evidence base	Completely revised

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the diagnosis and management of epilepsy in adults. It does not include patients with a non-epileptic attack disorder *(see section 3.3.1)*.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to all health professionals in primary and secondary care involved in the management of people with epilepsy, including general practitioners, practice nurses, epilepsy specialist nurses, general physicians, emergency department specialists, neurologists, obstetricians, clinical neuropsychologists and psychiatrists. It will also be of interest to those commissioning epilepsy services, public-health physicians, pharmacists, social-work staff, carers and relatives of people with epilepsy and people with epilepsy themselves.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally off-label prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[6]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[6]

The General Medical Council recommends that when prescribing a medicine off label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice, and
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[7]

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 11.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 DIAGNOSIS

C **The diagnosis of epilepsy should be made by an epilepsy specialist.**

C **A clear history from the patient and an eyewitness to the attack give the most important diagnostic information, and should be the mainstay of diagnosis.**

2.2 TREATMENT

Antiepileptic drugs should be offered after a first tonic-clonic seizure if:

B • **the patient has had previous myoclonic, absence or focal seizures**

B • **the EEG shows unequivocal epileptic discharges**

B • **the patient has a structural cerebral disorder**

D • **the patient considers the risk of recurrence unacceptable.**

C **Routine switching between different manufacturers of antiepileptic drugs should be avoided.**

C **Failure to respond to appropriate antiepileptic drugs should prompt a review of the diagnois of epilepsy and adherence to medication.**

B **Referral for assessment for neurosurgical treatment should be considered if the epilepsy is drug resistant.**

D **EEG should be used for confirming diagnosis of and monitoring treatment effects in patients with *status epilepticus*. EEG should be available as an emergency intervention for all patients with treated or suspected *status epilepticus*.**

2.3 MANAGEMENT OF PROLONGED SEIZURES INCLUDING *STATUS EPILEPTICUS*

✓ As soon as possible:

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure IV access in large veins.

B **Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given:**

- **midazolam 10 mg buccally or intranasally, or**
- **lorazepam 4 mg IV if midazolam is unavailable, or**
- **diazepam 10 mg if midazolam and lorazepam are unavailable.**

B **Administer a repeat dose of benzodiazepine in hospital after 10 minutes if there is no response.**

2.4 EPILEPSY AND WOMEN'S HEALTH

C **To minimise the risk of contraceptive failure, a woman using any combined hormonal contraception, or a combined oral contraceptive pill, or a progesterone-only pill should be prescribed an antiepileptic drug that does not induce hepatic enzymes.**

Women with epilepsy should:

B • **receive prepregnancy counselling at the time of diagnosis and at regular intervals during their management, especially if they are taking antiepileptic drug treatment**

D • **be reassured that most will have a normal pregnancy and delivery**

C • **have their diagnosis and treatment, if appropriate, reviewed by specialist services before conception; a concerted effort should be made to optimise seizure control and rationalise antiepileptic drug therapy prior to conception**

D • **be well informed about pregnancy and epilepsy-related issues, including smoking cessation, before conception.**

2.5 PSYCHIATRIC COMORBIDITY

D **Screening for depression and suicidality should be considered in all patients with epilepsy.**

2.6 MORTALITY

B **Healthcare professionals and patients should aim for complete seizure freedom to reduce the risk of sudden unexpected death in epilepsy.**

D **Adherence to the prescribed antiepileptic drug regime should be strongly encouraged and the patient asked to report any adverse effects that might compromise adherence in order to reduce the risk of increased mortality and morbidity.**

✓ Patients with active seizures, ie who have sustained seizures, and in particular generalised tonic-clonic seizures, in the past year, should be assessed by a specialist physician and epilepsy nurse specialist.

D **Counselling about the risks of sudden unexpected death in epilepsy should be considered for patients with epilepsy at an appropriate time for the patient and by an appropriate healthcare professional** (consultant neurologist, physician with an interest in epilepsy, specialist registrar, or epilepsy nurse specialist).

2.7 MODELS OF CARE

D **A structured management system for patients with epilepsy should be established in primary care. As with other chronic diseases, an annual review is desirable.**

3 Diagnosis

3.1 WHO SHOULD MAKE THE DIAGNOSIS OF EPILEPSY?

The diagnosis of epilepsy has important physical, psychosocial and economic implications for the patient. It is therefore important that the diagnosis is correct. It has been shown that a significant proportion of epilepsy diagnoses made by non-specialists are incorrect.[3,4] Epilepsy may be difficult to diagnose in the early stages,[8] especially in the absence of a witnessed account. Differentiation between epileptic seizures and stereotyped behavioural phenomena can be difficult in people with a learning disability. 2+

C **The diagnosis of epilepsy should be made by an epilepsy specialist.**

✓ The diagnosis of epilepsy is most appropriately delivered in the setting of a dedicated first-seizure or epilepsy clinic. Appropriate patient information should be given *(see section 10)*.

An epilepsy specialist has been defined as a trained doctor with expertise in epilepsy as demonstrated by training and continuing education in epilepsy, peer review of practice and regular audit of diagnosis. Epilepsy must be a significant part of their clinical workload (equivalent to at least one session a week).[9] 4

3.2 DEFINITION AND CLASSIFICATION

In 2014 the International League Against Epilepsy (ILAE) task force for the definition of epilepsy proposed that epilepsy be considered a disease of the brain defined by any of the following conditions:[10]

- at least two unprovoked (or reflex) seizures occurring more than 24 hours apart
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60% over the next 10 years), or
- diagnosis of an epilepsy syndrome.

The relevance of this definition to treatment decisions in clinical practice, however, is under discussion. In practice many healthcare professionals consider the practical definition of epilepsy, warranting treatment with antiepileptic drugs, as simply the first point of the definition above (ie the occurrence of at least two unprovoked seizures occurring more than 24 hours apart).

Classification of seizure types and epilepsy syndromes should always be attempted, as both may have implications for management and prognosis.

The ILAE classification systems for seizures and epilepsy syndromes remain the most widely used and recognised systems in clinical practice.[11,12]

An updated classification and organisational system was proposed by the ILAE in 2010, although this is evolving and undergoing refinements.[13] It is increasingly used in clinical practice, although has yet to be universally adopted.

A brief summary of these classifications systems is given below.

3.2.1 CLASSIFICATION OF EPILEPTIC SEIZURES (ILAE 1981)

International classification of epileptic seizures:[11]

I. Partial seizures

A. simple partial seizures (no loss of consciousness)

B. complex partial seizures

1. with impairment of consciousness at onset

2. simple partial onset followed by impairment of consciousnes

C. partial seizures evolving to generalised tonic-clonic (GTC) convulsions

II. Generalised seizures
(convulsive or nonconvulsive with bilateral discharges involving subcortical structures)

A. absence

B. myoclonic

C. clonic

D. tonic

E. tonic-clonic

F. atonic

III. Unclassified epileptic seizures
(usually used when an adequate description is not available)

3.2.2 CLASSIFICATION OF EPILEPSY SYNDROMES (ILAE 1989)

In this system,[12] the principal divisions are between focal epilepsies, in which seizures arise from a specific area of the brain, and generalised epilepsies, in which seizures arise in diffuse bilateral networks.

Focal and generalised epilepsies are themselves subdivided into idiopathic syndromes, which have a presumed genetic basis, and cryptogenic/symptomatic syndromes, in which a structural lesion is known or suspected (although may not always be visible on imaging).

3.2.3 UPDATED ORGANISATION SYSTEM FOR SEIZURES AND EPILEPSIES (ILAE 2010)

The updated classification system recognises that classification is challenging, as there is still insufficient knowledge to develop a fundamental framework on which to base a scientific classification. This system is designed to be an 'organisation' system (rather than a scientific classification), with a greater flexibility such that it can be useful both in clinical practice and in scientific research.

When used in clinical practice, however, this system is not dissimilar to the 1989 system, but with some key changes in nomenclature.[13]

- The terms 'simple partial seizure' and 'complex partial seizure' have been replaced by the term 'focal seizure'. Focal seizures in which consciousness is impaired are described as 'focal dyscognitive seizures'.
- The terms 'idiopathic', 'symptomatic' and 'cryptogenic' have been replaced by the terms 'genetic', 'structural-metabolic', and 'unknown'.

For the purposes of this guideline, the nomenclature of the updated (ILAE 2010) classification system has been used.

3.2.4 THE RELEVANCE OF CLASSIFICATION IN CLINICAL PRACTICE

It is important to make the distinction between genetic generalised epilepsies (GGEs, the new term for idiopathic generalised epilepsies) and focal epilepsies, as this affects treatment choices, investigation, prognosis and counselling. Identifying the aetiology is important in focal epilepsies.

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The onset of GGEs is unusual over the age of 25.[14] The most common GGEs in adolescence are juvenile myoclonic epilepsy (generalised tonic-clonic seizures with myoclonic seizures on waking, sometimes with absence seizures, with photoparoxysmal response in 30% of cases), early morning tonic-clonic seizures in adolescence, and juvenile absence epilepsy. These phenotypes may overlap.[15-19]

Features suggesting genetic generalised epilepsies are:

- childhood or teenage onset
- triggered by sleep deprivation and alcohol
- early morning tonic-clonic seizures or myoclonic jerks
- short absence seizures
- photoparoxysmal response on electoencephalography (EEG)
- generalised 3 per second spike and wave or polyspike and wave on EEG.

Features suggesting focal epilepsies are**:**

- history of potential cause
- aura
- focal motor activity during seizure
- automatisms.

C **The seizure type(s) and epilepsy syndrome should be identified.**

C **The distinction should be made between a focal epilepsy and a genetic generalised epilepsy.**

Tonic-clonic seizures without any focal features or any positive features of a genetic generalised epilepsy cannot be confidently classified.

3.3 CLINICAL FACTORS AND DIAGNOSIS

Attack disorders such as faint and epilepsy produce their effects because some element of physiology becomes disordered, temporarily disturbing the function of the brain. For a test to positively identify the nature of an attack disorder, an attack must be recorded, and the disturbed physiology detected. As this is usually impractical, the routine diagnosis of attack disorders is largely clinical, based on history. The history should make clear what occurred before, during and after the attack, from both patient and eyewitness points of view. A number of clinical features are common to different types of attack, so diagnosis should be based on the ensemble of the clinical features, not on single features. A generalised tonic-clonic seizure may be the presenting symptom in people with previously unrecognised epilepsy and a detailed history should be taken to uncover previous myoclonic, absence or focal seizures.[16, 20-30]

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C **A clear history from the patient and an eyewitness to the attack give the most important diagnostic information, and should be the mainstay of diagnosis.**

3.3.1 DIFFERENTIAL DIAGNOSIS OF EPILEPSY

Misdiagnosis of epilepsy is common, and can have major consequences. A full discussion of the differential diagnosis of epilepsy is beyond the scope of this guideline, but the conditions most frequently confused with epilepsy include:

Vasovagal syncope

This is the most common attack disorder presenting to hospital emergency departments,[31] and may be confused with seizures particularly if there is stiffening and jerking during the episode (convulsive syncope). Features such as a prior history of fainting, a postural trigger, a warning of lightheadedness and/or visual symptoms, a brief duration of irregular jerking (less than one minute), and a rapid recovery without postictal confusion should raise suspician of convulsive syncope.

Cardiac syncope

This is an uncommon but important cause of confusion with epilepsy; this diagnosis should not be missed due to the risk of sudden death from cardiac arrhythmia. Collapse with syncopal features but without warning, particularly if occurring on exercise, or in the context of a personal or family history of either congenital heart disease or sudden death, should raise suspicion of cardiac syncope.

Non-epileptic attack disorder

These are events (also known as psychogenic non-epileptic seizures, dissociative seizures or pseudoseizures) which clinically resemble or may be mistaken for epileptic seizures, but which are not accompanied by electrophysiological correlates, and which have a presumed or known psychological cause. There is no consensus as to the most appropriate name for such events, and for the purposes of this guideline the terms 'non-epileptic attacks' and 'non-epileptic attack disorder' are used. Features which should raise suspicion of non-epileptic attack disorder include prolonged duration (over five minutes), an episode of prolonged motionless collapse, rapid recovery, and treatment resistance to multiple antiepileptic drugs with normal investigations. Definitive diagnosis of non-epileptic attack disorder is often difficult, however, and for effective management objective proof (by recording episodes on video-EEG) may be helpful.

The list of conditions that may mimic seizures is long, and also includes migraine, parasomnias, movement disorders, metabolic disturbances, and panic disorder; consideration of these conditions, and their distinction from epilepsy, is beyond the scope of this guideline.

3.4 USE OF EEG IN THE DIAGNOSIS AND CLASSIFICATION OF EPILEPSY

3.4.1 INTERICTAL ELECTROENCEPHALOGRAPHY

Electroencephalography is often helpful in the diagnosis and classification of epilepsy.[16, 32] However, it is essential to understand the scope and limitations of the technique when requesting an EEG examination and subsequently evaluating an expert report on the recording.[3] Non-specific EEG abnormalities are relatively common, especially in older people, patients with migraine or psychotic illness and those taking psychotropic medication. Non-specific abnormalities should not be interpreted as supporting a diagnosis of epilepsy.

A normal EEG does not exclude a diagnosis of epilepsy. A single routine EEG recording will show definite epileptiform abnormalities in 29–38% of adults who have epilepsy. With repeat recordings this rises to 69–77%.[16, 33-36] The sensitivity is improved by carrying out an EEG soon after a seizure, and by recordings during sleep or following sleep deprivation.[16, 37, 38] 2^+

Incidental epileptiform abnormalities are found in 0.5% of healthy young adults, but are more likely in people with learning disability and psychiatric disorders, patients with previous neurological insult (for example head injury, meningitis, stroke, cerebral palsy), and patients who have undergone neurosurgery.[39-41]

In a patient in whom the clinical history suggests an epileptic seizure but is not conclusive, the likelihood of epilepsy will be high. The finding of epileptiform abnormalities is specific, and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, such as syncope, the likelihood of epilepsy will be low, and any epileptiform abnormalities are more likely to be incidental. The test should not be performed in this circumstance.

EEG can aid classification of epileptic seizures and epilepsy syndromes. The finding or not of a photoparoxysmal response can allow appropriate advice to be given.[42] If carried out within the first few weeks after a first seizure, EEG has prognostic value; patients with epileptiform abnormalities are more likely to have a second attack.[43] 2+

EEG is the gold standard investigation in the diagnosis of non-convulsive *status epilepticus (see section 4.10.4)*.

3.4.2 SHORT-TERM VIDEO-EEG

Inpatient videotelemetry remains the gold standard for the diagnosis of seizure disorders, but short-term outpatient EEG may enable definitive diagnosis of non-epileptic attack disorder without recourse to this if a typical attack can be recorded. Studies of short-term video-EEG report that a definitive diagnosis is obtained in 33–66% of individuals with non-epileptic attack disorder using this technique.[44, 45] The use of induction techniques, particularly suggestion, appears to increase the sensitivity of the investigation,[44, 46] but this has not been definitively established. 1- 3

3.4.3 LONG-TERM EEG MONITORING

When clinical information and standard investigations do not allow a confident diagnosis, referral for the recording of attacks should be considered. The attacks should usually be occurring at least once a week. If non-epileptic attack disorder is a possibility, then monitoring patients with less frequent attacks may be worthwhile, as attacks are often easily provoked.[47-54] The best method is inpatient video-EEG recording.[55] Twenty-four hour ambulatory EEG recording has the advantage of recording attacks in the patient's usual setting, but does not usually allow correlation of EEG and video data. 2+ 3 4

These investigations should include single channel electrocardiography recording.[56]

3.4.4 POLYSOMNOGRAPHY

Polysomnography (PSG) may be used to confirm a diagnosis of sleep-related epilepsy, although the sensitivity and specificity of this investigation have not been adequately assessed, and there is evidence that epileptic seizures are less reliably identified on standard PSG-EEG montages than on full video-EEG telemetry montages.[57, 58] Combined PSG with full video-EEG telemetry (video-EEG-PSG) may be helpful in the differential diagnosis of non-epileptic sleep disorders from nocturnal epilepsy,[59] but standard PSG, which is generally only undertaken for a single night compared to 96 hours for video-EEG telemetry, is likely to be inferior to videotelemetry in the diagnosis of epilepsy. 2+ 3

C **EEG is not routinely indicated and cannot exclude a diagnosis of epilepsy.**

C **EEG should be used to support the classification of epileptic seizures and epilepsy syndromes when there is clinical doubt.**

C **EEG should be performed in young people with generalised seizures to aid classification and to detect a photoparoxysmal response.**

B **Short-term video-EEG, preferably with suggestion, should be available for the investigation and diagnosis of suspected epilepsy and non-epileptic attack disorder.**

C **Inpatient video-EEG monitoring and other specialist investigations** (including polysomnography with full EEG montages) **should be available for patients who present diagnostic difficulties.**

✓ Access to urgent EEG (within 24 hours of request) should be available in all acute medical units for the diagnosis of suspected non-convulsive *status epilepticus.*

3.5 HAND-HELD VIDEO

There is good evidence that epileptic seizures can be distinguished from non-epileptic attack disorder based on the semiology alone (ie analysis of the behaviours observed during a seizure).[60] Onset of attacks is rarely recorded, however,[55, 61] and the sensitivity and effectiveness of hand-held video (for example smartphones) alone as a diagnostic test has not been assessed. Informed consent should always be obtained from the patient prior to asking others to videorecord the attacks. 1++

✓ Asking family members or friends to videorecord events should be considered in patients with uncertain diagnosis. Consent should always be sought in advance.

3.6 BRAIN IMAGING

Brain imaging detects lesions in 21–37% of patients presenting with epilepsy. Such lesions require treatment in only a small minority, but their detection may have implications for future management should the epilepsy become intractable. Genetic generalised epilepsies are not associated with an increased prevalence of brain lesions.[16, 62-65] 2+

3.6.1 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is the current standard of reference in the investigation of patients with epilepsy. Routine MRI of the brain using simple standard sequences will detect lesions (for example small tumours, vascular malformations and cortical dysplasia) that are not detected by computed tomography (CT). MRI carried out for the assessment of drug-resistant epilepsy requires specialised protocols and expertise (for example to detect hippocampal sclerosis) and should, ideally, be carried out by a neuroradiologist.[65-73] 2++ 2+ 4

3.6.2 COMPUTED TOMOGRAPHY

CT scanning has a role in the urgent assessment of seizures, or when MRI is contraindicated (for example when patients have pacemakers or metallic implants). A non-contrast CT scan will fail to identify some vascular lesions and tumours. CT has only a limited role in the assessment of intractable epilepsy.[66, 73, 74] 2++ 2+

C **MRI is the modality of choice for brain imaging in patients with epilepsy.**

C **Brain imaging is not routinely required when there is a confident diagnosis of a genetic generalised epilepsy.**

D **CT has a role in the urgent assessment of seizures, or when MRI is contraindicated.**

3.7 ELECTROCARDIOGRAPHY

Electrocardiography (ECG) should be carried out in the assessment of all patients with altered consciousness, particularly those in older age groups, when disorders of cardiac rhythm may simulate epilepsy. Twenty-four hour ambulatory ECG and other cardiovascular tests (including implantable loop devices) may also be helpful.[56] 3

✓ Patients who have blackouts, strange feelings, or 'funny turns' should have a 12-lead electrocardiogram.

3.8 GENETIC TESTING

The genetics of epilepsy is a large, and rapidly expanding field. While most genetically acquired epilepsies show a complex inheritance pattern (suggesting involvement of multiple genes and possibly environmental influences), an increasing number of monogenic epilepsy syndromes (ie epilepsy caused by a mutation in a single gene) are recognised.[75]

When assessing a patient with epilepsy a comprehensive history with particular focus on the family history should be taken, and an accurate epilepsy syndromic diagnosis made. While in most cases reassurance can be given that the risk of epilepsy developing in the children of parents with epilepsy is low *(see section 5.3)*, expert advice on the genetics of epilepsy should be available if required.

✓ A clinical genetics service, with expertise in the genetics of epilepsy, should be available to patients with a very strong family history of epilepsy, or with a clinical phenotype suggestive of a monogenic epilepsy syndrome.

4 Treatment

4.1 WHEN TO START ANTIEPILEPTIC TREATMENT

The crucial decision whether or not to start antiepileptic drug (AED) treatment must take into account the relative risks of recurrent seizures (including the small but important risk of SUDEP) and the commitment to long-term medication with potential adverse effects.

4.1.1 EPILEPSY

Antiepileptic drugs should not be given until the diagnosis of epilepsy has been confirmed *(see section 3)*. If there is uncertainty, a period of observation will usually clarify the epilepsy syndrome and confirm the need for treatment.[8, 9]

4.1.2 SINGLE SEIZURES

The patient's view on medication should be considered. Women planning a pregnancy may choose to avoid AEDs in the short term, though they must be warned of the attendant risks (*see section 5.2)*. Individuals wishing to avoid recurrent seizures, for example for driving, should be offered immediate treatment.

A detailed history should be taken to exclude previous myoclonic, absence or focal seizures as patients with undiagnosed epilepsy may present with a single generalised tonic-clonic seizure.[16]

Whether to treat a single seizure or not is largely decided by the risk of further seizures. Estimates of recurrence risk vary. Highest recurrence rates (up to 90%) are seen in patients with epileptic discharges on EEG or structural cerebral disorder. Lowest rates (13–40%) are associated with acute symptomatic seizures (provoked) or patients with a normal EEG and no identifiable cause for seizures.[43, 76-78] Overall the risk is 30–40%; this is greatest in the first twelve months and falls to <10% after two years.[79] 1+ 2++ 2+ 4

While treatment with AEDs after a single seizure has a short-term effect in reducing the recurrence risk,[80] this effect is not sustained.[81, 82] Early treatment with AEDs does not appear to alter the prognosis of epilepsy which is best predicted by the number of seizures in the first six months after diagnosis and response to first AED.[83-85]

B **The decision to start antiepileptic drugs should be made by the patient and an epilepsy specialist.**

Antiepileptic drugs should be offered after a first tonic-clonic seizure if:

B • **the patient has had previous myoclonic, absence or focal seizures**

B • **the EEG shows unequivocal epileptic discharges**

B • **the patient has a structural cerebral disorder**

D • **the patient considers the risk of recurrence unacceptable.**

4.2 ANTIEPILEPTIC DRUG MONOTHERAPY

The clinical classification of epilepsy along with the adverse effect and interaction profiles for an individual patient are key in determining initial monotherapy.[86, 87] The dose of each medication should be titrated slowly to the maximally tolerated dose or the maximum level as recommended in the British National Formulary.[6] Effect may be monitored by patient-recorded seizure frequency.

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

4.2.1 FOCAL EPILEPSY

In focal epilepsy lamotrigine is as effective and better tolerated than carbamazepine, topiramate, or oxcarbazepine.[86, 88] There is evidence from clinical trials for use of zonisamide and levetiracetam as monotherapy.[89, 90] Zonisamide is not approved by SMC for monotherapy for the treatment of focal seizures in adults with newly diagnosed epilepsy *(see section 11.4)*. Lamotrigine may have advantages for adolescents, young women *(see section 5)* and older people *(see section 4.14)* because it is well tolerated,[91-93] has a favourable cognitive and behavioural profile,[94] and does not lead to weight gain.[95] Controlled release formulations of carbamazepine may reduce the incidence of adverse effects.[96] 1++

4.2.2 GENETIC GENERALISED EPILEPSIES

In genetic generalised epilepsies, sodium valproate, topiramate and lamotrigine may be used.[87, 97] Of the three, sodium valproate is most effective.[87, 97] There is no randomised controlled trial (RCT) evidence that levetiracetam as monotherapy is superior to established first choice monotherapy with valproate but in some cases it may be a useful first choice, for example in women of reproductive age because of concerns about teratogenicity with some AEDs *(see section 5.6.3)*. Levetiracetam is not, however, currently licensed for use as monotherapy in generalised epilepsy. Ethosuximide has been used for absence seizures in children for many decades[98] and has been shown to have comparable efficacy to sodium valproate in this epilepsy type.[99] 1+

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

4.2.3 CHOICE OF FORUMLATION

Stable dosing with individual formulations (generic or branded) is less likely to be associated with worsening control than changing formulations of individual drugs.[100] Some studies suggest that changing between formulations may lead to variations in seizure control and increased utilisation of health resources.[100] Formulations of AEDs are not interchangeable and generic substitution should not be routinely made.[100, 101] 2+

A **In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives.**

A **In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug.**

A • **Where sodium valproate is poorly tolerated or contraindicated, lamotrigine and topiramate are suitable alternatives.**

D • **In women of childbearing age, levetiracetam or lamotrigine may be a reasonable alternative.**

C **Routine switching between different manufacturers of antiepileptic drugs should be avoided.**

✓ The adverse effect and interaction profiles should direct the choice of drug for the individual patient.

✓ Sodium valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and a Pregnancy Prevention Programme is in place.

4.3 MANAGEMENT OF DRUG-RESISTANT EPILEPSY

Drug-resistant epilepsy has been defined as failure to achieve sustained seizure freedom after trials of two tolerated and appropriate AED schedules (whether as monotherapies or in combination).[102]

The majority of patients with newly-diagnosed epilepsy respond well to AEDs. Failure to do so may be due to:

- an incorrect diagnosis of epilepsy[3, 103]
- an inappropriate choice of AED for the epilepsy syndrome[103, 104] 1++ 2+ 4
- failure to take the prescribed AED
- an underlying cerebral neoplasm, metabolic condition, or immune process
- concurrent drug or alcohol misuse.

Given a correct diagnosis of epilepsy, failure to control seizures completely with the first well-tolerated AED is a predictor of drug-resistant epilepsy.[85, 105] The choice of adjunctive AED will depend on a number of factors including sex, reproductive potential, age, concomitant medications, pre-existing or comorbid conditions, other medical or psychiatric conditions and adverse effect profiles. 2+

Once two AEDs have failed as monotherapy the chance of seizure freedom with further monotherapy is low.[85] Improvement in seizure control may be obtained by combining AEDs.[106, 107] 2++ 2+ 4

Once the decision has been made to use combination therapy, the patient should be established on the best combination at the optimal dose, ie one that produces best efficacy with fewest adverse effects.[108] A range of different AEDs appropriate to the epilepsy syndrome should be added as necessary in sequence, increasing the dose of each slowly to obtain the best response. Deciding on the best combination may be a matter of trial and error, although some evidence exists for enhanced efficacy of lamotrigine/sodium valproate[109] and lacosamide/non-sodium channel blocking drug.[110] 2+ 4

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

The aim should be seizure freedom on the lowest number of drugs. With good response, consideration should be given to withdrawal of the baseline AED. Where an encouraging but suboptimal effect is obtained with a particular combination, it may be worthwhile trying the addition of a small dose of a third AED.

The law of diminishing returns may require patient and doctor to accept the persistence of some seizures once a range of treatment options has failed and where surgery is not an option *(see section 4.9)*. Adequacy of seizure control must be balanced with optimal quality of life. Little will be lost by carefully reducing the drug burden in a patient with continuing seizure activity aiming for the most effective combination of two or at most three AEDs. Producing less intrusive episodes, abolishing tonic-clonic seizures, preventing falls and decreasing automatisms can be acceptable end points for some patients.

4.3.1 DRUG-RESISTANT FOCAL EPILEPSY

Meta-analysis has shown that carbamazepine, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate and zonisamide are all effective in the adjunctive treatment of focal epilepsy.[111, 112] Evidence for treatment with clobazam was limited with one systematic review reporting that it may reduce seizure frequency.[113] The ultimate choice will depend on individual patient factors as described in section 4.3. 1++ 1+

Tolerability issues may limit use of retigabine and tiagabine, with retigabine requiring careful monitoring to assess for skin and retinal changes.[114] While barbiturates can be cost-effective AEDs, their propensity for drug interactions, poor tolerance, and withdrawal seizures mean these should only be used in a specialist epilepsy clinic.[115] 4

Patients being treated with vigabatrin should have specific and careful monitoring by opthalmologists because of the risk of developing concentric visual field defects.[108]

Drug-resistant focal epilepsy associated with some primary conditions (for example intracranial tumours or paraneoplastic limbic encephalitis) may require multidisciplinary management, for example with oncology and neurology.

4.3.2 DRUG-RESISTANT GENERALISED OR UNCLASSIFIED EPILEPSY

RCTs have shown that lamotrigine,[97] levetiracetam,[97, 111] sodium valproate and topiramate[87] are all effective in the adjunctive treatment of generalised epilepsy. Ethosuximide remains useful in patients with absence seizures. Drop attacks in patients with Lennox-Gastaut syndrome may respond to rufinamide.[116] 1++

Lamotrigine acts synergistically with sodium valproate to produce a better therapeutic outcome.[109] Lacosamide was shown to be effective and well tolerated. Treatment response was good regardless of type of concomitant AED but when lacosamide was used in combination with a non-sodium channel blocker response rates were higher and adverse events less frequent.[110] 2+

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

C **Failure to respond to appropriate antiepileptic drugs should prompt a review of the diagnosis of epilepsy and adherence to medication.**

D **Combination therapy should be considered when treatment with two first-line antiepileptic drugs has failed or when improved control occurs during the process of phased substitution.**

A **Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy.**

A **Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy.**

B **The choice of drugs in combination should be matched to the patient's seizure type(s) and should, where possible, be limited to two or at most three antiepileptic drugs.**

✓ Sodium valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and a Pregnancy Prevention Programme is in place.

4.4 ANTIEPILEPTIC DRUG BLOOD LEVELS

There is no indication for routine monitoring of AED concentrations.[117-119] Evidence supports clinically useful dose-response and dose-toxicity relationships for carbamazepine and phenytoin. These relationships do not occur with sodium valproate or any of the newer AEDs. Phenytoin also undergoes saturation kinetics which can make accurate dosage adjustment without concentration monitoring problematical. Even with these two drugs, however, the upper and lower borders of the target ranges are imprecise and are not applicable to all patients.[117] 1+ 4

Blood level monitoring should be undertaken to answer a specific clinical question; does imperfect adherence to the treatment schedule explain the poor seizure control? Specialist knowledge is required to interpret assay results as the pharmacokinetics of some AEDs are non-linear and because of the pharmacokinetic interactions that may take place. This is particularly important given the lack of a useful target range for the majority of AEDs.[120]

In situations where drug metabolism is likely to change, measurement of AED blood levels may be useful, for example in pregnancy *(see section 5.4.2)*.

D **Routine monitoring of antiepileptic drug concentrations is not indicated. Measurement can sometimes be useful in the following circumstances:**

- **adjustment of phenytoin dose**
- **assessment of adherence**
- **assessment of toxicity**
- **situations where drug metabolism is likely to change, eg pregnancy**
- **otherwise unexplained loss of seizure control.**

✓ Antiepileptic drug blood level measurement is best supervised by an epilepsy specialist.

4.5 MANAGEMENT OF PROVOKED SEIZURES

Seizures can be provoked by acute metabolic disturbances, treatment with certain drugs *(see section 4.12)* and drug withdrawal (for example alcohol, benzodiazepines, barbiturates). Provoked seizures may occur in the context of drug misuse (alcohol, heroin, cocaine, methadone, amphetamine, ecstasy). The risk of recurrence of such provoked seizures can be reduced by correction or withdrawal of the provocative factor.

A systematic review reported the benefit from benzodiazepines compared to placebo in preventing seizures related to alcohol withdrawal, although this finding was based on only three studies (two of them very small), and a very small number of events. A trend in favour of benzodiazepines compared with other treatments for seizure control in this context was also shown.[121] Commencement of longer-term AED treatment is only indicated if unprovoked seizures occur.

Provoked seizures are defined as occurring within seven days of an acute condition such as encephalitis, head injury, cerebral infarction, craniotomy and cerebral haemorrhage. There is evidence that treatment can reduce the risk of such provoked seizures in the context of traumatic brain injury (by phenytoin and carbamazepine), craniotomy (by phenytoin) and cerebral malaria (by phenobarbital).[122, 123] There is no evidence, however, that prophylactic treatment of provoked seizures influences the subsequent development of epilepsy. In patients with acute traumatic brain injury, there is no evidence that early prophylaxis with AEDs influences other outcomes such as death and neurological disability.[123] If AED treatment is commenced following the occurrence of provoked seizures, it should be used only in the short term, unless unprovoked seizures occur later. 1+

Attacks occurring immediately after a concussive closed-head injury have been described as concussive convulsions. There is no evidence that these will recur and AED treatment is not indicated.[124] 3

✓ When seizures are provoked by metabolic disturbances or drugs, attention should be directed to correction or withdrawal of the provocative factor.

✓ Patients with seizures provoked by alcohol or substance misuse may benefit from referral to addiction services and other support agencies

B **Following an acute brain insult or neurosurgery, long-term prophylactic antiepileptic drug treatment is not indicated.**

C **Following an acute brain insult, antiepileptic drugs used to treat the provoked seizures should be withdrawn** (unless unprovoked seizures occur later).

D **Antiepileptic drug treatment is not indicated for concussive convulsions.**

4.6 ANTIEPILEPTIC DRUG ADVERSE EFFECTS

Antiepileptic drug adverse effects are common and a major cause of drug failure. Most are mild but a minority can be life threatening.[125-127] Accurate data on prevalence of adverse drug reactions (ADRs) with long-term AED treatment is scarce; almost all reports refer to short-term clinical trials and, as experience with vigabatrin and visual-field defects has shown, long-term surveillance is needed to identify all ADRs.[128] Older people are more sensitive to AED adverse effects *(see section 4.14)*. 1++ 1+ 3

4.6.1 DOSE-RELATED ADVERSE REACTIONS

Many AED adverse effects are dose-related and predictable. These can be minimised by gradual escalation of dose, with dose reduction if symptoms persist. Use of slow-release carbamazepine can reduce peak dose-related adverse effects of dizziness and blurred vision.[129]

4.6.2 IDIOSYNCRATIC ADVERSE DRUG REACTIONS

Idiosyncratic drug reactions usually occur in the first weeks of treatment and are potentially serious. Rash is the most common, occurring in up to 10% of patients on carbamazepine, phenytoin or lamotrigine. Most rashes are mild and resolve promptly on discontinuation of the AED, but severe cutaneous reactions are seen in up to 1 in 1,000 patients.[130-132] This incidence is increased if the initial dose is increased rapidly.[133] Genetic testing can help predict idiosyncratic drug reactions in some racial populations, for example carbamazepine reaction in Han Chinese and Caucasians.[134, 135] Patients of Asian descent should have human leucocyte antigen (HLA) status checked prior to starting carbamazepine. 2+ 4

The life-threatening AED hypersensitivity syndrome of fever, rash, lymphadenopathy and multiorgan failure occurs in up to 4.5 in 10,000 patients, mostly with carbamazepine, lamotrigine or phenytoin.[130] It is important to note that cross sensitivity occurs between these AEDs in up to 70% of patients. Rapid titration or drug interactions may make this more likely. 2+

Minor blood dyscrasias are associated with many AEDs; the majority (mild leucopenia with carbamazepine, thrombocytopenia with sodium valproate) require no action. Severe blood dyscrasia occurs in 6 in 10,000 patients but there is no evidence to suggest that routine monitoring is worthwhile.[136, 137] 2+ 4

Hyponatraemia (sodium <135 mmol/l) is seen in about 20% of patients taking carbamazepine or oxcarbazepine; it is usually well tolerated and of no significance.[138] If mild (>120 mmol/l) and asymptomatic this should not deter ongoing treatment with AEDs. It should be remembered that other drugs may have a role in reducing sodium levels and may be targets for reduction if sodium levels become troublesome.

Elevation of liver enzymes (γ-glutamyl transferase 90%, alkaline phosphatase 30%) is seen in people taking enzyme-inducing AEDs and is usually of no clinical significance.[139] Clinical symptoms have been shown to be more useful than routine monitoring of liver function in identifying the onset of serious ADRs.[137, 140] 4

Acute psychotic reactions are seen occasionally with vigabatrin, topiramate and tiagabine, particularly in those patients with a previous history of psychiatric disease; withdrawal from the drug usually results in recovery.[141]

4.6.3 CHRONIC SYSTEMIC ADVERSE EFFECTS

Some AEDs are associated with weight gain and some with weight loss. The effects of different AEDs on bodyweight may be influenced by factors such as treatment regimen (for example dosage, mono- or polytherapy) and other medications being taken by the patient. The possibility of weight gain or loss should be considered when agreeing treatment plans with patients.

Sedation and dizziness are common complaints of patients starting AED therapy but usually resolve with time.[126] Sedation may be less with AEDs licensed from, for example, 1990 onwards, particularly lamotrigine, oxcarbazepine and levetiracetam.[94] Many patients on long term AED therapy report cognitive adverse effects *(see section 4.6.5)* but studies to confirm this have been contradictory and confounded by the effects of chronic epilepsy.[142, 143] Polytherapy is probably associated with more cognitive adverse effects than monotherapy.[144] 1++ 2+ 4

Impaired bone health is associated with chronic epilepsy and its treatment, and this should be included in the counselling given near the time of diagnosis *(see section 4.6.4)*.

✓ Antiepileptic drugs should be commenced in a dose no higher than recommended by the manufacturer.

C **Patients should be warned of common potential adverse effects and given clear instructions to seek medical attention urgently for symptoms including rash, bruising or somnolence with vomiting especially in the first weeks of treatment.**

D **Liver function and full blood count should not be monitored routinely.**

4.6.4 BONE HEALTH

Antiepileptic drug use is associated with a higher risk of clinical fracture,[145-149] with one systematic review reporting that AEDs increased the odds of fracture by 1.2 to 2.4 times.[148] The evidence is strongest for an association with phenobarbital, carbamazepine, clonazepam and sodium valproate.[148, 149] Bone mineral density is also lower in these patients and many fractures are related to seizures.[148, 149] Postmenopausal women who use AEDs are at increased risk of fracture (hazard ratio (HR) 1.44, 95% CI 1.30 to 1.61)[145] and most AEDs were associated with an increased risk of non-traumatic factures in individuals aged 50 or over.[146] 2^+ 2^-

A systematic review found no RCTs investigating therapeutic agents to prevent fracture in people with epilepsy although one RCT included in the review suggested that supplementation with high dose vitamin D may be associated with increased bone mineral density in patients taking AEDs.[148] 2^+

A study comparing 150 people taking AEDs and 506 who were not found that fewer than 30% of patients with epilepsy know of the association between AEDs and fracture.[147] This is a significantly under-researched area.

C **Patients taking antiepileptic drugs should receive dietary and other lifestyle advice to minimise the risk of osteoporosis.**

4.6.5 PSYCHIATRIC AND BEHAVIOURAL ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS

A study of the beneficial and adverse psychotropic effects of AEDs in people with epilepsy found that levetiracetam, tiagabine, zonisamide, topiramate and vigabatrin were associated with primarily negative psychotropic effects. Psychoses have been reported with levetiracetam, tiagabine, topiramate and vigabatrin *(see section 6.2.2)*.[150]

Gabapentin, pregabalin and lamotrigine have been associated with positive psychotropic effects, especially with regard to affective symptoms.[150] 1^+

Methodological problems with some of the reported studies and the risk of confounding, however, mean that these results should be treated with caution.

B **The potential negative psychotropic effects of antiepileptic drugs should be borne in mind when deciding on the most appropriate antiepileptic drug treatment for an individual patient.**

✓ Antiepileptic drug treatment should be used with caution in those with pre-existing behavioural or psychiatric conditions and epilepsy.

4.7 ANTIEPILEPTIC DRUG WITHDRAWAL

Evidence of the risks of seizure recurrence after discontinuation of AEDs was provided by a large, multicentre, randomised, prospective trial of continued antiepileptic treatment versus slow withdrawal in adults and children with epilepsy who had been seizure free for at least two years.[151] AED withdrawal was associated with an increased risk of seizure recurrence, which was influenced by the duration of seizure freedom, the history of seizure types, the occurrence of one or more seizures after the start of the treatment and whether one, or more than one, AED was being taken. The data from the study were used to develop a prognostic index for seizure recurrence.[152] This has been used to calculate the risks of seizure recurrence with continued treatment or with slow AED withdrawal *(see Tables 1 and 2).* An abnormal EEG at the time of entry into the study was associated with only a small increased risk of seizure recurrence. Since this is unlikely to influence a decision about whether or not to withdraw AED treatment in adults, EEG recording is not necessary for an informed decision to be made. The higher risks of seizure recurrence with a history of myoclonus reflect the high risk of seizure recurrence following AED withdrawal in juvenile myoclonic epilepsy. The prognostic index has not been validated on an external population, and should be used with caution. 1^{++}

No information is available on the risks of seizure recurrence following drug withdrawal in adults who have been seizure free for less than two years, although for children the risks are higher after less than two years of seizure freedom than for more than two years.[153]

The effect of different rates of AED withdrawal on the risk of seizure recurrence has not been adequately studied.

Important factors influencing a decision about AED withdrawal in adults include driving, employment, fear of further seizures, risks of injury or death with further seizures and concerns about prolonged AED treatment. The Driver and Vehicle Licensing Agency recommendations should be followed.[154]

A **Prognostic index indicators can be used to give an estimate of the risks of seizure recurrence following antiepileptic drug withdrawal.**

✓ The question of continued treatment or antiepileptic drug withdrawal should be discussed with people with epilepsy who are at least two years seizure free, so that they can make an informed choice. Factors to be discussed should include driving, employment, fear and risks of further seizures and concerns about prolonged antiepileptic drug treatment.

✓ The rate of withdrawal of antiepileptic drugs should be slow, usually over a few months, and longer with barbiturates and benzodiazepines. One drug should be withdrawn at a time.

4.8 COMPLEMENTARY THERAPY

Complementary therapy is increasingly popular with patients, who may use this in addition to conventional medication.[155, 156] The term covers a wide variety of treatments such as acupuncture, chiropractic treatment, herbal medicine, homeopathy, osteopathy, yoga, traditional Chinese medicine and cannabinoids. There is no consistent evidence to support, or definitively exclude, the use of any particular type of complementary therapy to improve seizure frequency in patients with epilepsy. Findings from systematic reviews covering a range of approaches including meditation techniques,[157] acupuncture,[158] cognitive behaviour therapy,[159] yoga,[159, 160] and relaxation therapy,[159] were inconsistent or not generalisable to a Scottish population (for example for acupuncture) and the quality of the included studies was often poor. Systematic reviews of RCTs looking at the use of traditional Chinese medicine[161] and cannabinoids[162] found only poor quality studies and concluded that there was insufficient evidence to support the use of either of these approaches in the treatment of epilepsy. 1^{++} 1^{+} 2^{++}

Patients should be asked if they are using any complementary medicines and warned about the possibility of adverse effects. Problems may arise with the use of some herbal medicines because of interaction with prescribed medication. The potential reduction of the plasma concentrations of carbamazepine, phenobarbital and phenytoin should be noted if St John's wort is used concomitantly.[163] The British National Formulary advises against this. Caution is also advised in the use of evening primrose oil but the evidence for this is less robust. 4

Some aromatherapy preparations (for example hyssop, rosemary, sweet fennel, sage and wormwood) may have an alerting effect on the brain and so may exacerbate seizures.[164, 165]

Table 1: Prognostic index for recurrence of seizures after remission of epilepsy for patients taking only one antiepileptic drug[152]

Risk of seizure recurrence by two years (%)																				
Period free from seizures	2 years			4 years			6 years			8 years			10 years			15 years				
Seizure history*	TC	My	Oth	TC	My	Oth	TC	My	Oth	TC	My	Oth	TC	My	Oth	TC	My	Oth		
Seizures after start of AED therapy:																				
Current EEG unavailable	35	50	25	20	35	15	20	30	15	20	25	15	15	25	10	15	25	10		
	60	75	45	40	60	30	35	55	25	35	50	25	35	50	25	30	45	25		
Current EEG abnormal	35	50	25	25	35	15	20	30	15	20	30	15	20	25	15	15	25	10		
	60	80	50	45	60	35	40	55	30	35	50	25	35	50	25	30	45	25		
Current EEG normal	30	45	20	20	30	15	15	25	10	15	25	10	15	25	10	15	20	10		
	55	70	40	35	55	30	30	45	25	30	45	20	30	45	20	25	40	20		
No seizures after start of AED therapy:																				
Current EEG unavailable	25	40	20	15	25	10	15	20	10	15	20	10	10	20	10	10	20	10		
	45	65	35	30	45	25	25	40	20	25	40	20	25	35	20	20	35	15		
Current EEG abnormal	25	40	20	15	25	10	15	25	10	15	20	10	15	20	10	10	20	10		
	50	65	35	35	50	25	30	40	20	25	40	20	25	40	20	25	35	20		
Current EEG normal	20	35	15	15	20	10	10	20	10	10	20	10	10	15	10	10	15	10		
	40	60	30	30	40	20	25	35	20	20	35	15	20	35	15	20	30	20		

*TC: history of genetic or secondary generalised tonic-clonic seizures
My: history of myoclonic seizures with tonic-clonic seizures (myoclonic seizures rarely occur alone)
Oth: history of seizures other than tonic-clonic or myoclonic

Table 2: Prognostic index for recurrence of seizures after remission of epilepsy for patients taking more than one antiepileptic drug[152]

Period free from seizures	**Risk of seizure recurrence by two years (%)**																					
	2 years			4 years			6 years			8 years			10 years			15 years						
Seizure history*	TC		My	Oth	TC		My	Oth	TC		My	Oth	TC		My	Oth	TC		My	Oth	TC		My	Oth
Seizures after start of AED therapy:																						
Current EEG unavailable	50	75	65	40	35	60	50	25	30	55	45	20	25	50	40	20	25	45	35	20	30	15
Current EEG abnormal	50	80	70	90	40	65	35	60	50	80	25	50	30	55	45	25	30	50	40	20	35	15
Current EEG normal	45	70	60	85	35	60	30	55	45	70	20	40	25	45	40	20	25	45	35	15	30	15
No seizures after start of AED therapy:																						
Current EEG unavailable	40	65	55	80	30	50	25	45	40	65	20	35	35	60	15	30	20	40	30	15	30	15
Current EEG abnormal	40	65	55	85	30	55	25	50	40	65	20	35	35	60	15	30	20	40	30	15	30	15
Current EEG normal	35	60	50	75	25	45	20	40	35	60	15	30	30	55	15	25	20	35	25	10	25	10

*TC: history of genetic or secondary generalised tonic-clonic seizures
My: history of myoclonic seizures with tonic-clonic seizures (myoclonic seizures rarely occur alone)
Oth: history of seizures other than tonic-clonic or myoclonic

4.9 SURGICAL REFERRAL

Neurosurgical procedures are an effective treatment for some patients with epilepsy resistant to drug treatment *(see section 4.3)*.[166, 167] It is important that surgery be considered as soon as it is established that the epilepsy is drug resistant, as the benefits will be greater in younger patients. Some neurosurgical procedures involve resection of part of the brain, and the aim is to obtain complete seizure freedom. For the most commonly performed procedures, involving anterior and medial temporal lobe resection, about 70% of patients will become seizure free.[168] Other procedures are palliative and include callosotomy, subpial transection, vagus nerve stimulation (VNS)[169] *(see section 4.9.1)* and direct brain stimulation *(see section 4.9.2)*. Assessment for suitability for surgery should be carried out in a specialist unit. For each individual the potential benefits of improved seizure control, quality of life and possible reduction in antiepileptic medication need to be balanced against the risks of the surgical procedure. 1+

B **Referral for assessment for neurosurgical treatment should be considered if the epilepsy is drug resistant.**

D **Assessment as to suitability for a potentially curative resective procedure should be made before consideration of palliative procedures such as vagus nerve stimulation.**

4.9.1 VAGUS NERVE STIMULATION

Evidence from four systematic reviews suggests that VNS is an effective and relatively safe treatment in patients with medically refractory epilepsy,[170-173] although the usefulness of one review may be limited because of concerns about the quality of the included studies.[171] One systematic review, however, comparing VNS with continued or modified AED therapy, failed to find sufficient evidence of superiority of effectiveness or net benefit in medically refractory epilepsy, with complete seizure freedom rarely achieved using VNS and a quarter of patients receiving no benefit from therapy.[170] Adverse effects reported in one review were found to differ from those for AEDs and included hoarseness, cough, pain, paresthesias and dyspnea, although these appeared to be reasonably well tolerated as dropouts were rare.[172] Cost implications of VNS relating to implantation, battery replacement and monitoring of the device and the potential limitation on subsequent MRI investigation should be taken into account when VNS is being considered. 1++ 2-

C **Vagus nerve stimulation may be considered in adult patients who have been found to be unsuitable for resective surgery**

4.9.2 DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) has been used to treat patients with drug-resistant epilepsy who are not candidates for surgery. In one RCT in adults, DBS seemed to reduce seizure frequency, but the trial had substantial limitations.[174]

4.9.3 TRANSCRANIAL MAGNETIC STIMULATION AND TRIGEMINAL NERVE STIMULATION

There is insufficient evidence on which to base a recommendation for these modes of non-pharmacological treatment.[175]

4.10 MANAGEMENT OF PROLONGED SEIZURES INCLUDING *STATUS EPILEPTICUS*

Most seizures remit spontaneously without intervention. If spontaneous cessation does not occur, then management should be escalated.

Definitions of *status epilepticus* are varied with minimum durations of either five or 30 minutes.[176] Trial protocols involve intervention being indicated after five minutes of seizure.[177] For the purposes of this guideline all prolonged seizures are grouped together.

Emergency treatment should be sought or given once a seizure has persisted, or there are serial seizures, for five minutes or more. Generalised tonic-clonic *status epilepticus* is a medical emergency with significant morbidity and a mortality of between 16% and 39%.[178] Both morbidity and mortality can be exacerbated by inadequate or delayed treatment.[179-181] Treatment by paramedics after five minutes of tonic-clonic seizure leads to a better outcome than waiting until the patient arrives at the emergency department before starting treatment.[182-184] Non-convulsive *status epilepticus*, including focal and absence *status epilepticus* may be clinically subtle enough to have delayed diagnosis and treatment, but have a much lower risk of morbidity. Prompt and accurate differentiation of *status epilepticus* from pseudo-*status epilepticus* and other non-epileptic disorders is crucial if inappropriate treatment and iatrogenic morbidity are to be avoided.[179, 185] 1++ 3

As seizures and sedative drugs can reduce levels of consciousness and because seizure activity does not always cause overt clinical movement, EEG recording is the best method of confirming the diagnosis and assessing treatment response when seizures are clinically subtle, for example in non-convulsive *status epilepticus (see section 4.10.4)* or following treatment of tonic-clonic *status epilepticus*.[186] Non-availability of EEG may lead to over-treatment of *pseudo-status epilepticus* and/or prolongation of sedation and ventilation. 3

D **EEG should be used for confirming diagnosis of and monitoring treatment effect in patients with *status epilepticus*. EEG should be available as an emergency intervention for all patients with treated or suspected *status epilepticus.***

✓ Non-availability of EEG should not deter or delay treatment of patients with *status epilepticus*.

Patients who are prone to prolonged seizures require specific management *(see section 4.11)*.

4.10.1 IMMEDIATE MEASURES

Once five minutes of seizure activity have passed, treatment should be given as quickly as possible. Initial management of such prolonged seizures should be with benzodiazepines. [187] Studies have examined the comparative efficacy and tolerability of midazolam, lorazepam and diazepam. While there is no definitive benefit shown for individual benzodiazepines or modes of administration, choice of route or specific benzodiazepine will be determined by ease and rapidity of administration, access to appropriately stored drug, and patient dignity. Benzodiazeines are safe when given by non-medical staff in an out-of-hospital setting.[182] 1++

The efficacy and safety of intramuscular (IM) midazolam and intravenous (IV) lorazepam is similar, although ease of administration and ease of storage may favour midazolam (lorazepam requires temperature controlled storage).[184] Intramuscular midazolam is not currently licensed for use in patients with *status epilepticus.*

Administration of midazolam via the buccal or intranasal route is not currently licensed in adults and evidence for its use is limited. A meta-analysis (six studies, five in paediatric populations) concluded that non-IV midazolam was safe and effective compared to diazepam in treating patients with *status epilepticus*. Three of the studies reported greater effectiveness of buccal midazolam than rectal diazepam, but three reported no difference between non-IV midazolm and IV diazepam.[176] Two small studies comparing buccal midazolam with rectal diazepam in adults in residential settings showed similar efficacy between the two but greater acceptability of buccal midazolam.[188, 189] 1++ 1+ 2+

On the basis of evidence in children of ease of use, rapid access, effectiveness and patient dignity, the guideline development group consider that buccal/nasal midazolam is the preferred first-line treatment in adults.[176, 190] Direct evidence for the effectiveness of buccal/intranasal midazolam compared with IV lorazepam is currently lacking. 1++

✓ As soon as possible:

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure IV access in large veins.

B **Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given:**

- **midazolam 10 mg buccally or intranasally, or**
- **lorazepam 4 mg IV if midazolam is unavailable, or**
- **diazepam 10 mg IV or rectally if midazolam and lorazepam are unavailable.**

4.10.2 IN-HOSPITAL TREATMENT (FOLLOWING FAILURE OF INITIAL BENZODIAZEPINE)

If seizures continue despite initial dosing with a benzodiazepine, a second dose of benzodiazepine should be administered in a clinical setting. Where two doses of benzodiazepines have failed, additional maintenance treatment with other AEDs is required. Intravenous phenytoin has been the traditional choice, but there is some evidence from head-to-head trials that sodium valproate has similar efficacy with fewer adverse effects,[191, 192] although the studies were small and at risk of bias. Some smaller studies have suggested usefulness of IV levetiracetam on comparison with lorazepam or sodium valproate.[193, 194] 1+ 1-

The use of sodium valproate is contraindicated in pregnancy and in women and girls of childbearing potential *(see section 5.2.0)*.[454] In an emergency, the balance of risks and benefits means that the prime consideration is to provide optimal and rapid control of seizures. For maintenance or long-term treatment, the MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential should be followed where possible. Specialist review of women and girls of childbearing potential currently using sodium valproate should be initiated following successful resolution of the seizure and continued use of sodium valproate in this group should be avoided *(see also section 5)*.

B **Administer a repeat dose of benzodiazepine in hospital after 10 minutes if there is no response.**

✓
- Collect blood for a full blood count, urea and electrolytes, liver function tests, calcium, glucose, clotting, antiepileptic drug levels and storage for later analyses.
- Measure blood gases to assess the extent of acidosis.
- Establish aetiology. Give 50 ml of 50% glucose IV if there is any suggestion of hypoglycaemia and IV thiamine (given as Pabrinex, two pairs of ampoules) if there is any suggestion of alcohol misuse or impaired nutritional status.

✓ For sustained control in patients with established epilepsy give the usual antiepileptic drug treatment orally or by nasogastric tube (or IV if necessary for phenytoin, sodium valproate, phenobarbital, levetiracetam or lacosamide).

D **Within 30 minutes, if seizures continue:**

- **give sodium valproate 20–30 mg/kg IV 40 mg/min, or phenytoin 18 mg/kg IV 50 mg/min with ECG monitoring. Rates of phenytoin infusion may need to be reduced if hypotension or arrhythmia occur in older people or where there is renal/hepatic impairment.**

✓ If the patient remains unresponsive after initial treatment, EEG should be utilised to differentiate between continued seizures and drug-induced sedation *(see section 4.10)*.

✓ Clear policies should be in place to avoid confusion between doses, formulations, routes and rates of administration of fosphenytoin and phenytoin.

4.10.3 SEIZURES PERSISTING LONGER THAN 30 MINUTES

If seizures persist the patient needs to be admitted to an intensive treatment unit (ITU) and anaesthetised with EEG monitoring to differentiate whether the reduced level of consciousness is seizure- or AED-induced *(see section 4.10)*. Midazolam, pentobarbital (unlicensed), propofol or thiopentone are most commonly used in these circumstances.[195] 4

D **If *status* persists, then within 60 minutes:**
- **admit the patient to an intensive treatment unit and administer general anaesthesia**
- **refer for specialist advice.**

D **EEG should be used to determine response to treatment.**

4.10.4 NON-CONVULSIVE *STATUS EPILEPTICUS*

Clinical manifestations of seizures change with persistence; convulsive movements become minimal or disappear. This may lead to diagnostic difficulty in differentiating reduced level of consciousness due to seizure from that caused by sedative or anaesthetic drugs. Persistence of seizure activity is perilous.

As with diagnosis of non-epileptic pseudostatus and clinically subtle seizures, EEG monitoring of treatment and response of non-convulsive *status epilepticus* is important *(see section 4.10)*.

✓ Patients with non-convulsive *status epilepticus* should be managed as follows:
- maintain or reinstate usual oral antiepileptic drug treatment
- consider benzodiazepine treatment (midazolam 10 mg buccally or intranasally, lorazepam 4 mg IV, or diazepam 10 mg IV)
- refer for specialist advice.

D **EEG should be used for diagnosing and monitoring treatment response in patients with non-convulsive *status epilepticus*.**

✓ Non-availability of EEG should not deter or delay treatment of patients with non-convulsive *status epilepticus*.

4.11 PATIENTS WITH RECURRENT PROLONGED OR SERIAL SEIZURES IN THE COMMUNITY

In some patients, epilepsy is so severe that the occurrence of severe or prolonged seizures is likely to be frequent. In such cases, carers of patients with recurrent prolonged or serial seizure episodes in the community may be able to terminate the seizure episode, prevent the development of *status epilepticus* and avoid unnecessary hospital admission by the administration of buccal or intranasal midazolam 10 mg,[176,196,197] or rectal diazepam 10–20 mg[198,199] close to seizure onset. Buccal/intranasal midazolam is not, however, currently licensed for use in adults and evidence for its use by carers is derived from studies in children and adolescents. An agreed and individual written administration protocol set by the specialist team should be followed.[200, 201] The protocol should be a clear written instruction that includes the indications for administering rescue medication, the maximum dose in 24 hours, the drug name, strength, dose and frequency, the route of administration, and when to call for emergency help and transfer to hospital. The protocol should be reviewed regularly for efficacy and appropriate usage. | 1^{++} 1^{+} 1^{-} 3

Carers should receive recognised training on how to follow the administration protocol and the reasons for using rescue medication. Where applicable, they should be encouraged to record seizure episodes, outcomes and the use of rescue medication in the patient's care plan.[200-202] | 4

B **Patients with recurrent prolonged or serial seizures in the community should be initially managed by carers who should give midazolam 10 mg buccally or intranasally, or diazepam 10–20 mg rectally according to an agreed administration protocol.**

D **All carers of patients with epilepsy who may require buccal midazolam or rectal diazepam should receive recognised training in its administration.**

D **Where a care plan is required, it should be drawn up in consultation with the GP and/or specialist service, used by everyone working with the individual patient, and reviewed at regular intervals.**

✓ Protocols for rescue medication should be reviewed regularly and may be withdrawn or amended where such plans have not been enacted after a prolonged period.

4.12 DRUGS WHICH EXACERBATE EPILEPTIC SEIZURES

Both prescription and illicit drugs can occasionally precipitate seizures particularly in patients with epilepsy.[203] Causality is not always certain and may be multifactorial.

Mechanisms by which drugs may trigger seizures may include:

- lowering of the seizure threshold. This is usually dose/plasma concentration dependent and factors such as renal impairment (eg pethidine) or coadministration of interacting drugs (eg ciprofloxacin/ theophylline) may contribute
- decrease in AED levels via pharmacokinetic drug interactions (eg hepatic microsomal enzyme induction with rifampicin)
- effects secondary to other medical causes precipitated by drugs (eg drug-induced hyponatraemia or serotonin syndrome)
- individual AEDs which themselves may cause worsening of some types of seizures[104]
- drug withdrawal, eg from AEDs, alcohol, benzodiazepines, barbiturates and baclofen.[204, 205]

3
4

✓ All healthcare professionals should be vigilant for prescription of drugs that may cause or exacerbate seizures in patients with epilepsy.

✓ A wide variety of drugs has been reported to precipitate or potentiate seizures in patients with or without a history of epilepsy. Such theoretical risks should not preclude treatment of recognised comorbidities. Treatment of comorbid psychiatric conditions is covered in section 6.2.

4.13 MANAGEMENT OF PATIENTS WITH EPILEPSY IN THE PERIOPERATIVE PERIOD

Loss of seizure control due to missed oral medication can occur in the context of surgery, labour, and when there is difficulty in swallowing. Sometimes changes in drug doses or frequency will be necessary due to pharmacokinetic differences between formulations. Patients should be reviewed on a case-by-case basis and advice sought from a pharmacist regarding the most suitable alternative preparations, taking into consideration the varying pharmacokinetic drug profiles and route of administration.

✓ Healthcare professionals should consider the possible consequences of missed antiepileptic drug doses when planning hospital admission.

✓ Antiepileptic drugs should be administered by alternative routes or by giving additional doses as appropriate. When patients have been designated nil by mouth prior to surgery, they should still be given their usual oral antiepileptic drug unless absorption is impaired.

✓ When a prolonged problem with administration of drugs not available parenterally is anticipated, and oral or enteral administration is not possible, consideration should be given to seizure prophylaxis with parenterally available agents.

✓ Following surgery, the dosage of antiepileptic drug must be checked and confirmed prior to discharge.

4.14 MANAGEMENT OF OLDER PEOPLE WITH EPILEPSY

Old age is now the commonest time to develop epilepsy in the Western world. The annual incidence is 85.9 per 100,000 for people aged 65–69 years and 135 per 100,000 for those aged over 80 years.[206] The diagnosis of epilepsy presents unique difficulties in this age group. Older people with epilepsy have a mortality rate 2–3 times higher than the general population.

4.14.1 RISK FACTORS

Dementia and neurodegenerative disorders are estimated to account for 10–20% of all epilepsies in older people, and patients with Alzheimer's disease are up to ten times more likely to develop epilepsy than those without the condition.[207, 208] Cerebrovascular disease and stroke are important risk factors for developing epilepsy. Stroke can account for up to 50% of cases where a cause can be identified, and the risk of epilepsy increases up to 20-fold in the first year after a stroke.[207] In an older person with new-onset seizures, it is therefore important to undertake cognitive function screening and assessment for the presence of cerebrovascular risk factors with an appropriate treatment thereafter. A number of cognitive screening tools exist although none has been tested specifically in older people with epilepsy.[209] 3 4

In the view of the guideline development group the Abbreviated Mental Test Score may be suitable for use in a busy epilepsy clinic,[210] although other tools, such as the Addenbrook's Cognitive Assessment could be used where time and resources allow *(see section 6.2.3)*.[211]

4.14.2 PRESENTATION

Characteristics of presentation can vary later in life. Data suggest that, compared with younger patients, older patients are more likely to have a seizure arising from sleep, focal seizures without generalization, remote symptomatic aetiology, focal changes on EEG and an epileptogenic lesion on neuroimaging.[212]

4.14.3 ANTIEPILEPTIC DRUG TREATMENT

Antiepileptic drug treatment can be complicated by the frequent coexistence of epilepsy and dementia, comedication, and the increased likelihood of dose-related and idiosyncratic adverse effects. In this population, the use of carbamazepine is limited by its enzyme inducing properties, implicating the AED in a range of pharmacokinetic interactions.[213] The drug also has a propensity to cause hyponatraemia, particularly in patients taking diuretics.[214]

Studies examining initiation of AED treatment in older people found no significant difference in efficacy between normal-release carbamazepine, lamotrigine and gabapentin. However, in those with newly diagnosed focal-onset seizures lamotrigine and gabapentin had a better tolerability profile than normal-release carbamazepine,[215] and lamotrigine was better tolerated than sustained-release carbamazepine.[216] This was also the case for levetiracetam when compared with sustained-release carbamazepine in those with seizures following a stroke.[217] Levetiracetam produced fewer cognitive adverse effects than lamotrigine or phenobarbital in older patients with epilepsy and Alzheimer's disease.[217] Low-dose topiramate (25–50 mg daily) may also be useful as mono- or adjunctive therapy in older people, although adverse effects including somnolence, dizziness, headache and cognitive-related events have been reported.[218] 1^{++} 1^{+}

Until recently there has been a dearth of research on epilepsy in older people, but the situation is slowly changing. With appropriate management, older people with epilepsy appear to have a better prognosis than younger adults, with a significantly higher percentage becoming seizure free, often on lower AED doses.[219]

✓ Any older person developing new-onset seizures should undergo cognitive function screening and assessment for the presence of cerebrovascular risk factors, with appropriate management thereafter.

✓ When choosing an antiepileptic drug for an older person with newly diagnosed epilepsy, consideration of the following is paramount:

- adverse effect profile
- appropriate formulation
- dosing regimen in those with adherence issues
- drug interactions
- low starting dose
- slow titration schedule
- low maintenance dosing.

B **Lamotrigine or possibly levetiracetam should be considered when starting antiepileptic drug treatment in older people with focal-onset seizures.**

C **Gabapentin is an alternative mono- or adjunctive therapy option in older people with epilepsy.**

✓ For older people with cognitive problems, an epilepsy care plan should be considered.

4.14.4 QUALITY OF LIFE IN OLDER PEOPLE WITH EPILEPSY

Despite a growing appreciation of the importance of quality of life (QoL) issues in the management of epilepsy, little empirical guidance is available for older people.[220] Studies on health-related quality of life (HRQoL) are heterogeneous. Existing data suggest that although older people might cope better with the diagnosis of epilepsy,[221] they feel stigmatised by the condition, with seizure frequency being a significant predictor of impaired HRQoL.[222] 1+ 3

✓ Clinicians should be aware of the potential impact of epilepsy on HRQoL in older people with epilepsy.

✓ Further research is needed regarding quality of life issues in older people with epilepsy.

4.15 MANAGEMENT OF PEOPLE WITH LEARNING DISABILITY AND EPILEPSY

People with learning disability and epilepsy should have access to the same range of investigations and treatment as the rest of the population.[223, 224] All sections of this guideline are, therefore, relevant to people with learning disability, in particular those on management of prolonged seizures *(see section 4.10)* and mortality in epilepsy, including SUDEP *(see section 8)*. 4

Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

Epilepsy associated with learning disability is common with the prevalence highest (about 50%) in people with severe disability and cerebral palsy.[225] In some adults with learning disability it may be difficult to distinguish epilepsy from psychiatric illness, emotional and behavioural states and where doubts exist, videorecording of the episode, with appropriate consent, may help to secure diagnosis.[224, 226] 4

Quality of life in people with learning disability and epilepsy may be affected because of injuries sustained during seizures and because of the adverse effects of medication.[227] In situations where RCTs, of appropriate design, have been performed, it has been shown that adverse effects of AEDs in people with a learning disability are similar to those of the general population and that behavioural adverse effects are rare.[228] Seizure freedom is an appropriate endpoint for many people with learning disability and epilepsy. 1++ 4

The confidential enquiry into premature deaths of people with a learning disability found that, within the NHS, people with learning disabilities continue to have poor experience and outcomes compared to those without and an excess mortality has also been reported.[229] The government response to this enquiry makes several recommendations including emphasising the need to make reasonable adjustment for any individual to enable them to effectively access care.[230] 4

Clinical guidelines exist for the management of epilepsy in adults with an intellectual disability.[231, 232] In situations where the person cannot give informed consent, treatment may need to be given under the provisions of the Adults with Incapacity (Scotland) Act 2000.

In adults with Down's Syndrome, seizures can be a presenting symptom of dementia and over 80% of people with Down's Syndrome and dementia develop seizures. The most common type of seizures in these patients are generalised tonic-clonic seizures and myoclonic seizures although other seizure types may be seen. Guidelines exist for the management of epilepsy in those with Down's Syndrome and dementia.[233]

D **People with learning disability should be treated with the same range of antiepileptic drugs as the general population.**

✓ In the management of people with learning disability and epilepsy:

- adequate time should be allowed for the consultation
- the carer should know the patient and bring relevant information on seizure type, frequency, possible adverse effects of medication, general health and behaviour to the consultation
- information in an accessible form should be available to patients and carers
- there should be a multidisciplinary approach to treatment, delivered by professionals with an expertise in epilepsy, to improve quality of life
- community learning disability nurses have an important role in liaising between the specialist services and patients and carers.

✓ In people with Down's Syndrome and dementia who develop seizures, quality of life, including negative impact of all seizure types and medication adverse effects, should guide treatment.

✓ The quality of information brought to appointments is highly variable and therefore the validity of this information should be thoroughly checked.

5 Epilepsy and women's health

Women with epilepsy of childbearing potential need advice about contraception and pregnancy as well as information about epilepsy management. Those who have received such advice are likely to have more reliable contraception, better health during pregnancy and improved pregnancy outcomes.[234] In addition to seizure type or syndrome, the choice of AED for women may be influenced by factors including potential teratogenicity, interactions with hormonal methods of contraception, and potential cosmetic adverse effects.

In the UK, despite modern advances in epilepsy and obstetric management, epilepsy remains one of the leading contributors to maternal mortality.[235]

In September 2018, this section was updated to reflect new drug safety advice from the Medicines and Healthcare products Regulatory Agency (MHRA), issued in April 2018, on use of valproate medicines and women and girls of childbearing potiental *(see section 5.2.0)*.[454]

5.1 CONTRACEPTION

For women with epilepsy, advice on methods of contraception should be given early, ideally before they become sexually active. Advice should be based on a full understanding of the pharmacokinetics of AED treatment and the possibility of drug interactions. To avoid contraceptive failure, worsening seizures or neurotoxicity, when practical, these women should be offered contraceptive methods that do not interact with their AED treatment.

Contraceptive pathways for women with epilepsy are summarised in Figure 1. Postpartum contraception is covered in section 5.7.1. Methods of emergency contraception are discussed in section 5.1.2

For women with epilepsy, advice on hormonal contraception depends largely on the AED regimen, in particular, its hepatic enzyme-inducing characteristics.[236] AEDs can broadly be divided into those which induce hepatic enzymes (thus reducing the efficacy of some contraceptives) and those which do not *(see Table 3)*. 1+

Table 3: Action of AEDs on hepatic enzymes[213]

AEDs which induce hepatic enzymes (and reduce efficacy of some contraceptive methods)	**Non-enzyme inducing AEDs**
carbamazepine	acetazolamide
eslicarbazepine acetate	clobazam
oxcarbazepine	clonazepam
perampanel (≥12 mg daily)	ethosuximide
phenobarbital	gabapentin
phenytoin	lacosamide
primidone	*lamotrigine
rufinamide	levetiracetam
topiramate (≥200 mg daily)	pregabalin
	retigabine
	sodium valproate
	tiagabine
	vigabatrin
	zonisamide

* Combined hormonal contraceptives affect the metabolism of lamotrigine *(see section 5.1.1)*

Women with epilepsy receiving hepatic enzyme-inducing AEDs *(see Table 3)* are at risk of contraceptive failure if any form of combined hormonal contraception is used.[236] Those taking the combined oral contraception pill (COCP) are at increased risk of breakthrough bleeding and contraceptive failure, estimated at up to 7 per 100 woman years, due to accelerated oestrogen metabolism.[236-239] If there is no option but to use a COCP with a hepatic enzyme-inducing AED, the risk of breakthrough bleeding can be reduced by using a COCP containing a minimum of 50 micrograms ethinyl oestradiol increasing to 70 micrograms if breakthrough bleeding occurs.[240] Even with these measures there is a risk of pregnancy, and expert opinion advises 'tricycling', ie taking three packs of the high dose COCP consecutively and reducing pill-free days to four *(see Figure 1)*.[241] Enzyme induction can last for 14–28 days after withdrawl of the AED.[213] 1+ 2- 4

Enzyme-inducing AEDs increase progesterone metabolism and should not, therefore, be prescribed with either the progesterone-only oral contraceptive, the etonogestrel implant or the levonorgestrel implant.[236, 242] Progesterone injections and the levonorgestrel intrauterine system can be used with enzyme-inducing AEDs although there is some evidence that depot medroxyprogesterone acetate is associated with a reduction in bone mineral density.[243] 1+ 2+ 4

5.1.1 LAMOTRIGINE

Although lamotrigine is not thought to affect the efficacy of COCPs,[244] circulating lamotrigine concentrations are halved through glucuronidation induction by COCPs containing ethinyloestradiol/levonorgestrel.[236] Healthcare professionals should warn patients about this and be aware that lamotrigine dosing may need to be altered accordingly if these two medications are used together. This effect is negated when lamotrigine is prescribed with sodium valproate which inhibits lamotrigine glucuronidation. 1+

One small study in women taking progestogen-only contraception reported a 20–100% increase in lamotrigine circulating concentrations in women receiving the AED with desogestrel.[245] If these medications are prescribed together, women should therefore be counselled about the possibility of neurotoxicity symptoms. 3

✓ Advice on contraception should be given to young women, ideally before they become sexually active.

✓ For women with epilepsy not receiving antiepileptic drugs and for those receiving antiepileptic drugs that do not induce hepatic enzymes (other than lamotrigine), contraceptive options are the same as those for women in general.

C **To minimise the risk of contraceptive failure, a woman using any combined hormonal contraception, or a combined oral contraceptive pill, or a progesterone-only pill should be prescribed an antiepileptic drug that does not induce hepatic enzymes.**

D **For women receiving hepatic enzyme-inducing antiepileptic drugs:**

- **the levonorgestrel intrauterine system may be used without restriction**
- **depot injections of progestogen may be used without restriction and with no alteration to the normal dosing/replacement interval**
- **progestogen-only oral contraceptives are not recommended**
- **progestogen implants** (levonorgestrel and etonogestrel) **are not recommended**
- **if there is no alternative to a COCP, the COCP should contain at least 50 micrograms daily of oestrogen; if the COCP contains less oestrogen, the woman should be warned that the efficacy is reduced and additional barrier methods should be used**
- **if breakthrough bleeding occurs with a COCP containing 50 micrograms of oestrogen, the COCP dose should be increased to a maximum of 70 micrograms and 'tricycling' should be considered**
- **if the antiepileptic drug is withdrawn, it is important to note that enzyme induction persists for up to four weeks. Contraceptive cover should be ensured during this time.**

D **Women with epilepsy receiving lamotrigine:**

- **can use progestogen-only contraceptives without restriction. These women should be made aware of signs and symptoms of lamotrigine toxicity, and have the lamotrigine dose reduced if these occur.**
- **and combined hormonal contraceptives should be counselled about the reduction in circulating lamotrigine concentrations and the potential for, and consequences of, increased seizure activity. The healthcare professional should also discuss the possibility of increasing the lamotrigine dose with the patient.**
- **and combined hormonal contraceptives should be warned about signs and symptoms of lamotrigine toxicity if the contraceptive is withdrawn. A reduction in lamotrigine dosing may be necessary at this time.**

✓ Further research examining the use of lamotrigine with hormonal contraception is required.

5.1.2 EMERGENCY CONTRACEPTION

Options for emergency contraception for women with epilepsy depend on whether or not the woman is taking an enzyme-inducing AED. Women who are not taking AEDs or who are taking non-enzyme inducing AEDs can use emergency contraception as for women in the general population.

Hepatic enzyme-inducing AEDs increase the metabolism of levonorgestrel and ulipristal acetate. Current guidance recommends that ulipristal acetate should be avoided in women taking hepatic enzyme-inducing AEDs and that levonorgestrel, if used, is prescribed at double the normal dose, although this is outwith the current product licence.[246]

Healthcare professionals caring for women with epilepsy should discuss individual needs and inform women of the methods available to them. Information on efficacy, adverse effects, interactions, medical eligibility and need for additional contraceptive precautions should be included.[247]

4

D **Women with epilepsy who are not taking antiepileptic drugs, or who are taking non-enzyme inducing antiepileptic drugs, including lamotrigine, can use emergency contraception as for the general population.**

D **Women with epilepsy who require emergency contraception while using enzyme-inducing antiepileptic drugs, or who have stopped taking these within the last 28 days:**

- **should be prescribed a single dose of levonorgestrel 3 mg** (as opposed to 1.5 mg)**, ideally as soon as possible, and within 72 hours of unprotected intercourse**
- **should not be offered ulipristal acetate** (ellaOne®) **because of a risk of reduced efficacy**
- **may be offered insertion of a non-hormonal intrauterine device within 5 days of intercourse as an alternative option.**

Figure 1: Proposed management approach for women and teenage girls with epilepsy treated with antiepileptic drugs - contraceptive pathway

<table>
<tr><th colspan="2">Contraception advice</th></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td>Enzyme-inducing AED
• Carbamazepine
• Eslicarbazepine acetate
• Oxcarbazepine
• Perampanel (≥12 mg/day)
• Phenobarbital
• Phenytoin
• Primidone
• Rufinamide
• Topiramate (≥200 mg day)</td><td>Non-enzyme inducing AED
• Acetazolamide
• Clobazam
• Clonazepam
• Ethosuximide
• Gabapentin
• Lacosamide
• Lamotrigine
• Levetiracetam
• Perampanel (<12 mg/day)
• Pregabalin
• Retigabine
• Sodium valproate
• Tiagabine
• Topiramate (<200 mg/day/)
• Vigabatrin
• Zonisamide</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td>Hormonal
• Combined oral contraceptive pill must have at least 50 micrograms/day oestrogen
• If breakthrough bleeding occurs with no other obvious cause, consider increasing to 70 micrograms/day and tricycling
• Progesterone-only pill, progesterone implant, combined contraceptive patches, vaginal ring are not recommended due to reduced efficacy
• Depot/subcutaneous progesterone and levonorgestrel intrauterine system are suitable for use as efficacy is maintained
• Risk of bone loss with depot/subcutaneous progesterone
Non-hormonal
• Barrier is less effective than combined oral contraceptive pill
• Non-hormonal intrauterine device may be contraceptive of choice
Emergency contraception
• Single dose of levonorgestrel 3mg as soon as possible within 72 hours of unprotected intercourse
• Ulipristal acetate is not recommended due to reduced efficacy
• Insertion of a non-hormonal intra-uterine device within 5 days of intercourse is an alternative</td><td>Hormonal
• As for women not taking an AED
• Non-enzyme inducing AEDs do not alter the effectiveness of combined contraceptive patches, combined oral contraceptive pill, progesterone-only pill, progesterone implant, vaginal ring, or emergency contraceptives
• Lamotrigine clearance is doubled by ethinyloestradiol/levonorgestrel 30 micrograms/150 micrograms, threatening seizure control; an increased lamotrigine dose may be required
• Desogestrel may increase lamotrigine concentrations
Non-hormonal
• As for women not taking an AED
Emergency contraception
• As for women not taking an AED</td></tr>
</table>

Adapted from: the Epilepsy Expert Group - Clinical management algorithm for women and girls with epilepsy treated with antiepileptic drugs[248]

5.2 PRECONCEPTUAL COUNSELLING

Women with epilepsy who are of childbearing potential should be reviewed by specialist services prior to conceiving. This gives an opportunity to review the diagnosis and seizure control, discuss AED adherence and SUDEP risk, rationalise AED therapy, prescribe folic acid and discuss genetic factors.[234] 2+

The success of prepregnancy counselling is determined by a combination of access to care, attitudes, and the social context of the woman. Identifying women with epilepsy at risk of unplanned pregnancy and tailoring counselling accordingly may reduce adverse outcomes.[249] The provision of information during regular structured reviews in primary care is also important *(see section 9.1)*. 3

Prepregnancy counselling of women with epilepsy should encompass *(see Annex 2)*:

- reassurance that the majority of women with epilepsy will have a normal pregnancy and delivery[250]
- reassurance that the majority of women will be seizure-free during pregnancy and that those who are seizure-free prior to becoming pregnant are likely to remain seizure-free during pregnancy[251] 2++ 3 4
- advice on continuing AED treatment during pregnancy at the recommended doses, as poor adherence during pregnancy can lead to problems with seizures[252]
- advice on smoking cessation for women with epilepsy who smoke, as smoking in this population is associated with a substantially higher risk of premature contractions, pre term labour and delivery compared with women with epilepsy who do not smoke.[251]

Women with epilepsy should:

B • **receive prepregnancy counselling at the time of diagnosis and at regular intervals during their management, especially if they are taking antiepileptic drug treatment**

D • **be reassured that most will have a normal pregnancy and delivery**

C • **have their diagnosis and treatment, if appropriate, reviewed by specialist services before conception; a concerted effort should be made to optimise seizure control and rationalise antiepileptic drug therapy prior to conception**

D • **be well informed about pregnancy and epilepsy-related issues, including smoking cessation, before conception.**

5.2.0 SODIUM VALPROATE

In April 2018 the Medicines and Healthcare products Regulatory Agency (MHRA) issued new drug safety advice stating that valproate medicines must no longer be used in women or girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and there is no suitable alternative treatment, as judged by a specialist experienced in the management of epilepsy. Valproate medicines are teratogenic and can cause physical birth defects in babies and neurodevelopmental disorders in children born to mothers taking valproate *(see section 5.6)*.[454] A Patient Guide and supporting documents are available from MHRA.

Due to these concerns and the concomitant need to avoid pregnancy, the MHRA recommends that all female patients taking valproate medicines are supported on a Pregnancy Prevention Programme, that ensures they:

- have been told and understand the risks of use in pregnancy and have signed a Risk Acknowldgement Form[454]
- are on highly effective contraception if necessary[454]
- see their specialist at least every year.[454]

This condition applies unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.[454]

✓ Where sodium valproate is prescirbed for women or girls of childbearing potential,:

- a pregnancy test should be carried out beforehand to exclude pregnancy (unless there are compelling reasons to indicate that there is no risk of pregnancy)
- the lowest dose possible should be used.

5.2.1 FOLIC ACID

Women with epilepsy taking AEDs are at increased risk, compared to the general population, of having a child with neural tube defects (NTDs) and other malformations which may be related to altered folate metabolism.[253-255] The prevalence of congenital abnormalities is higher with sodium valproate than with other AEDs and rises with increasing number of AEDs taken *(see section 5.6)*.[256] 2++ 2+ 3

As for all women, those with epilepsy should take daily folic acid from preconception and throughout the first trimester of pregnancy.[256-261] There is increasing evidence from pregnancy registers to suggest that taking folic acid preconceptually and for at least the first 12 weeks of pregnancy may reduce the incidence of major congenital malformations in the offspring of women with epilepsy, particularly those receiving AED treatment,[256, 260-262] although not all studies show a relationship.[259, 263] In women receiving sodium valproate, folic acid may also significantly reduce the rate of spontaneous miscarriage, with a non-significant reduction for carbamazepine.[264] A prospective multicentre study of cognitive outcomes at age six in children of women prescribed sodium valproate, lamotrigine, carbamazepine or phenytoin monotherapy, reported that mean IQs were higher in children whose mothers had taken preconceptual folate, than in those who had not, but concluded that these results should be interpreted with caution as information on folate was obtained from mothers via a retrospective interview.[265] 2+ 4

Although there are insufficient data to guide dosing,[266] given that several AEDs are folate antagonists high dose folic acid, at 5 mg daily, is generally recommended for women with epilepsy receiving AED treatment.[267] For women with epilepsy not taking AEDs, folic acid should be given as recommended for women without epilepsy (400 micrograms daily), unless they have a family history of or a previous child with a neural tube defect, or a body mass index >30, when 5 mg daily should be taken.[268-270] 1++ 2+ 4

Certain AEDs, in particular phenytoin and phenobarbital, may exert their teratogenic effect through mechanisms other than depletion of folic acid.[259, 263] Research into these mechanisms is required. 2+

C **Women with epilepsy trying to conceive or who present in the first trimester should be advised to take folic acid during this time to reduce the risk of major congenital malformations.**

D **Women receiving sodium valproate should be advised that folic acid supplementation may reduce the rate of spontaneous miscarriage.**

Folic acid dosing:

A **400 micrograms daily for:**

- **women with epilepsy not receiving antiepileptic drug treatment**

5 mg daily for:

D
- **women with epilepsy receiving antiepileptic drug treatment**

A
- **women with epilepsy not on antiepileptic drug treatment, but with a family history of or a previous child with a neural tube defect**

A
- **women with epilepsy not on antiepileptic drug treatment, but with a BMI >30.**

✓ Research into the mechanisms underlying antiepileptic drug-associated teratogenic effects is required.

5.3 RISKS OF INHERITING EPILEPSY

Epilepsy is a heterogeneous disorder resulting from multiple genetic and non-genetic factors.[271] Chromosomal and single gene disorders causing epilepsy are rare. Over the past few decades, much progress has been

made in the field of epilepsy genetics. Risk prediction for most patients and families relies on results of epidemiologic studies which look at the risk of epilepsy in family members of individuals with the condition.

Mothers with epilepsy have higher rates of having affected offspring (2.8–8.7%) compared to fathers with epilepsy (1.0–3.6%).[272] The risks of passing on epilepsy are higher for mothers with genetic than with symptomatic epilepsies.

Parental age at onset of epilepsy also predicts risk to offspring. Parents with onset of epilepsy before the age of 20 have a 2.3–6% risk of having offspring with epilepsy; onset after age 20 confers a 1.0–3.6% risk. No increased risk to offspring of individuals has been found with epilepsy beginning after age 35.[273] The risk increases with the number of affected individuals in each family, and is also raised if there are specific EEG abnormalities in family members.

5.3.1 GENETIC GENERALISED EPILEPSIES

The reported risk of inheriting GGEs varies from study to study. A retrospective study gives risk of any type of seizure in a child of a mother with GGE as 4–8%; in a child of a father with GGE, the risk is only slightly higher than that for the general population.[30] When more than one first-degree relative is affected the risk of a child being affected is higher, sometimes approaching 30% or more. Another study of first-degree relatives found that for an affected individual, risk of GGE in a sibling was 2.5–6.7% and for children was 1.6–6.3%.[274]

The genetic contribution to epilepsy appears limited to epilepsy with onset aged under 35 years.[273, 275] Multiple genes influence the phenotypes of genetic generalized epilepsy.[276] Genetic susceptibility in patients with GGE increases the risk of epilepsy associated with cerebral palsy. Photosensitive genetic epilepsy is inherited in an autosomal dominant manner with age-dependent penetrance of the photoparoxysmal response. During maximum penetrance between the ages of 5 and 15, 50% of children of a photosensitive parent, will be photosensitive.[277]

2+
3
4

5.3.2 FOCAL EPILEPSIES

In relatives of patients with non-genetic focal epilepsy, there is no evidence for a significantly increased risk of epilepsy.[273, 275] In genetic focal epilepsies the risks are higher. For example, in parents with autosomal dominant nocturnal frontal lobe epilepsy the risk of a child developing this disorder may be up to 50%, depending on penetrance.[278]

2+
3
4

5.3.3 FEBRILE CONVULSIONS

Susceptibility to febrile convulsions also follows a multifactorial polygenic mode of inheritance with a maternal preponderance in transmission. There is a 27% risk in a child with an affected mother and 6% with an affected father.[279] Population-based studies indicate that 2–7% of children with febrile seizures will go on to develop epilepsy with afebrile seizures, the risk being higher with complicated febrile convulsions.[28]

3
4

5.3.4 RECENT GENETIC ADVANCES

Novel technologies and international collaboration have resulted in identification of new genes for monogenic and complex genetic epilepsies as well as risk factors for adverse effects of AEDs. There is the promise of further major advances in the years ahead which may allow more accurate prediction of inheritance risk, enhancing a new dimension to epilepsy management.[75]

For all patients with epilepsy, a comprehensive family history of epilepsy should be taken and expert advice on the genetics of epilepsy should be available as required.

✓ For most patients, reassurance can be given that, in general, the risk of epilepsy developing in the children of parents with epilepsy is low.

5.4 PREGNANCY

Epilepsy is a common maternal neurological disorder requiring management during pregnancy[281] and population-based studies estimate that 0.7% of pregnancies occur in women with the condition.[282] In Scotland, this equates to 400 births per year in women with epilepsy (based on 2011 data)[283] or 35 babies per year in a maternity unit with 5,000 births annually. Information on pregnancy outcomes and factors which may influence these pregnancy outcomes is important for counselling women during pregnancy and the puerperium. 3

A proposed management approach for women and girls treated with AEDs is shown in Figure 2.

Preconceptual counselling is important for all women with epilepsy and should include review by specialist services *(see section 5.2)*. The need to review AED use is heightened by the teratogenic nature of some AEDs, particularly sodium valproate. Safety advice issued by MHRA, in April 2018, on use of valproate medicines in women and girls of childbearing potential should be taken into account along with the conditions of the Pregnancy Prevention Programme *(see section 5.2.0)*.[454]

✓ Pregnancies in women with epilepsy should be supervised in an obstetric clinic with access to an obstetrician with a special interest in medical disorders in pregnancy and an epilepsy specialist.

5.4.1 SEIZURE CONTROL DURING PREGNANCY

In women with epilepsy, there are no data comparing seizure control in pregnancy to that of non-pregnant women.[251] Evidence suggests that in the majority of women with epilepsy, seizure frequency during pregnancy is improved or unchanged,[250, 282, 284] and 50% or more are seizure free throughout pregnancy.[262, 285-287] 2^{++} 2^{+}

Women with epilepsy who are seizure free for nine months or more prior to becoming pregnant are likely to remain seizure free (84–92%) during pregnancy.[251] Seizure control is more likely to be a problem in women with focal-onset than with primary generalized seizures (47% *v* 58.7% recurrence),[250, 288] and women taking polytherapy during pregnancy are more likely to have seizures than those taking monotherapy.[250, 286, 287] 3

Maternal morbidity and mortality

Although uncommon, the risks to a woman of injury and, rarely, death as a consequence of seizures persist in pregnancy.[235, 289] In the UK, epilepsy remains one of the leading contributors to maternal mortality and between 2009 and 2012 was associated with 14 maternal deaths during pregnancy and up to six weeks post partum, a rate of 0.40 per 10,000 pregnancies (95% CI 0.22 to 0.68). Twelve of these maternal deaths were due to SUDEP, two in women in single rooms in hospital.[235] Most of the 14 women who died did not receive preconceptual counselling and half of the women were not referred to an epilepsy specialist during pregnancy, despite a known history of epilepsy. In addition, a further 12 women with epilepsy died between six weeks and one year after the end of their pregnancy, two from drowning, six from SUDEP and four following other complications of seizures. 3

The frequency of *status epilepticus* in women with epilepsy during pregnancy is 0.55% to 1.8%.[250, 251, 284] The condition is associated with fetal as well as maternal mortality *(see section 4.10)*. There is insufficient evidence to determine if this rate of *status epilepticus* differs to that in non-pregnant women with epilepsy.[251] 2^{++} 3 4

D **As good seizure control during pregnancy is more likely in women whose seizures are controlled prior to becoming pregnant an effort should be made to optimise seizure control prior to pregnancy** (particularly for generalised tonic-clonic seizures).

✓ Women with epilepsy who are pregnant or who have recently been pregnant and who require hospital admission should not be placed in a single room.

5.4.2 AED DOSES AND BLOOD LEVEL MONITORING DURING PREGNANCY

Pregnancy is associated with pharmacokinetic changes including an increase in the volume of drug distribution, an increase in drug metabolism through hepatic microsomal enzyme induction, a reduction in serum albumin concentration and an increase in renal clearance.[290] There is a tendency for plasma levels of AEDs to fall during pregnancy, particularly for lamotrigine and levetiracetam,[287, 291, 292] but the implications for seizure control and frequency are difficult to predict. 3 4

The value of plasma AED monitoring in pregnancy is uncertain. Total plasma levels may be misleading and the relationship between free AED levels and seizure control is complex.[287, 293] Plasma level monitoring may occasionally be of use when there is concern about toxicity or adherence to therapy.[294]

Phenytoin circulating concentrations tend to correlate with seizure control and measurement can be worthwhile.[293] Recent data suggest poor seizure control and epilepsy-related death might be more common for patients receiving lamotrigine as opposed to other monotherapies, and that a more robust approach to adjusting lamotrigine dosing at this time is required.[250, 295] As lamotrigine clearance increases throughout pregnancy, monitoring of circulating lamotrigine concentrations, although not widely available, may also be a useful tool to aid adjustment of dose during pregnancy and in the postpartum period.[291, 296, 297] 2^+ 3 4

Further research is needed to determine best practice in managing lamotrigine dosing in pregnant women with epilepsy.

D **In pregnancy, dosing adjustment for the majority of antiepileptic drugs** (with the exception of lamotrigine and levetiracetam) **should only be considered if there is a change in seizure frequency or if toxicity is suspected.**

D **Healthcare professionals should be aware that the dose of lamotrigine may need to be increased during pregnancy. To avoid postpartum neurotoxicity, the lamotrigine dose should be reduced early in the puerperium.**

✓ As AED concentrations may fall during pregnancy, healthcare professionals need to be aware that dosing may need to be increased.

✓ If seizure control deteriorates during pregnancy, other factors affecting AED levels in pregnancy should be considered (for example vomiting, interactions with other medication).

✓ For pregnant women with epilepsy, routine monitoring of AED concentrations is not indicated. However, the measurement of AED concentrations can be useful in the following circumstances: for adjustment of phenytoin dose, assessment of AED adherence and suspected AED toxicity.

✓ The interpretation of AED blood levels is best performed by an epilepsy specialist.

✓ Issues relating to AED blood level monitoring must be discussed with the patient.

5.4.3 PREGNANCY COMPLICATIONS

Evidence comparing obstetric complications during pregnancy in women with or without epilepsy is inconclusive.

In women with epilepsy there is insufficient evidence to support or refute:[251]

- an increased risk of pregnancy-induced hypertension
- an increased risk of pre-eclampsia in those taking AEDs.

2^{++}

One UK study found that the general obstetric complication rate (comprising vaginal bleeding, urinary infection, hypertension, breech presentation, fetal distress and multiple pregnancy) was higher in women with treated epilepsy than controls, but not for any single complication.[262]

Hepatic enzyme-inducing AEDs *(see Table 3)* increase the metabolism of corticosteroids used for the prevention of neonatal respiratory morbidity. Women taking hepatic enzyme-inducing AEDs who require antenatal corticosteroids should, therefore, receive double the normal dose.[213] 2++

Recommendations for administration of vitamin K_1 to infants born to women with epilepsy do not differ from those for all infants and 1 mg of intramuscular vitamin K_1 at birth should be offered, unless there are contraindications.[298] If there are additional risk factors for haemorrhagic disease of the newborn (for example maternal liver disease, anticipated premature delivery), consideration should be given to the administration of oral vitamin K_1 (phytomenadione at 10 mg daily) in the third trimester of pregnancy.[299] 4

D **Pregnant women with epilepsy receiving hepatic enzyme-inducing antiepileptic drugs who require antenatal corticosteroids for the prevention of neonatal respiratory morbidity, should receive double the standard dose of betamethasone/dexamethasone** (48 mg over 12–24 hours).

D **All infants of women with epilepsy should be offered vitamin K_1, 1 mg intramuscularly at birth, unless there are contraindications.**

D **If there are additional risk factors for haemorrhagic disease of the newborn** (for example maternal liver disease, anticipated premature delivery) **consideration should be given to the maternal administration of oral vitamin K_1** (phytomenadione 10 mg daily) **in the third trimester of pregnancy.**

5.5 LABOUR AND BIRTH

Most women with epilepsy will have a normal labour and a vaginal delivery at term.[252, 262, 300] Stress, pain, sleep deprivation, overbreathing and dehydration increase the risk of seizures during labour and birth. If tonic-clonic seizures occur during labour, maternal hypoxia, fetal hypoxia and acidosis may result. 2++ 3 4

✓ Women with epilepsy should be delivered in a consultant-led maternity unit.

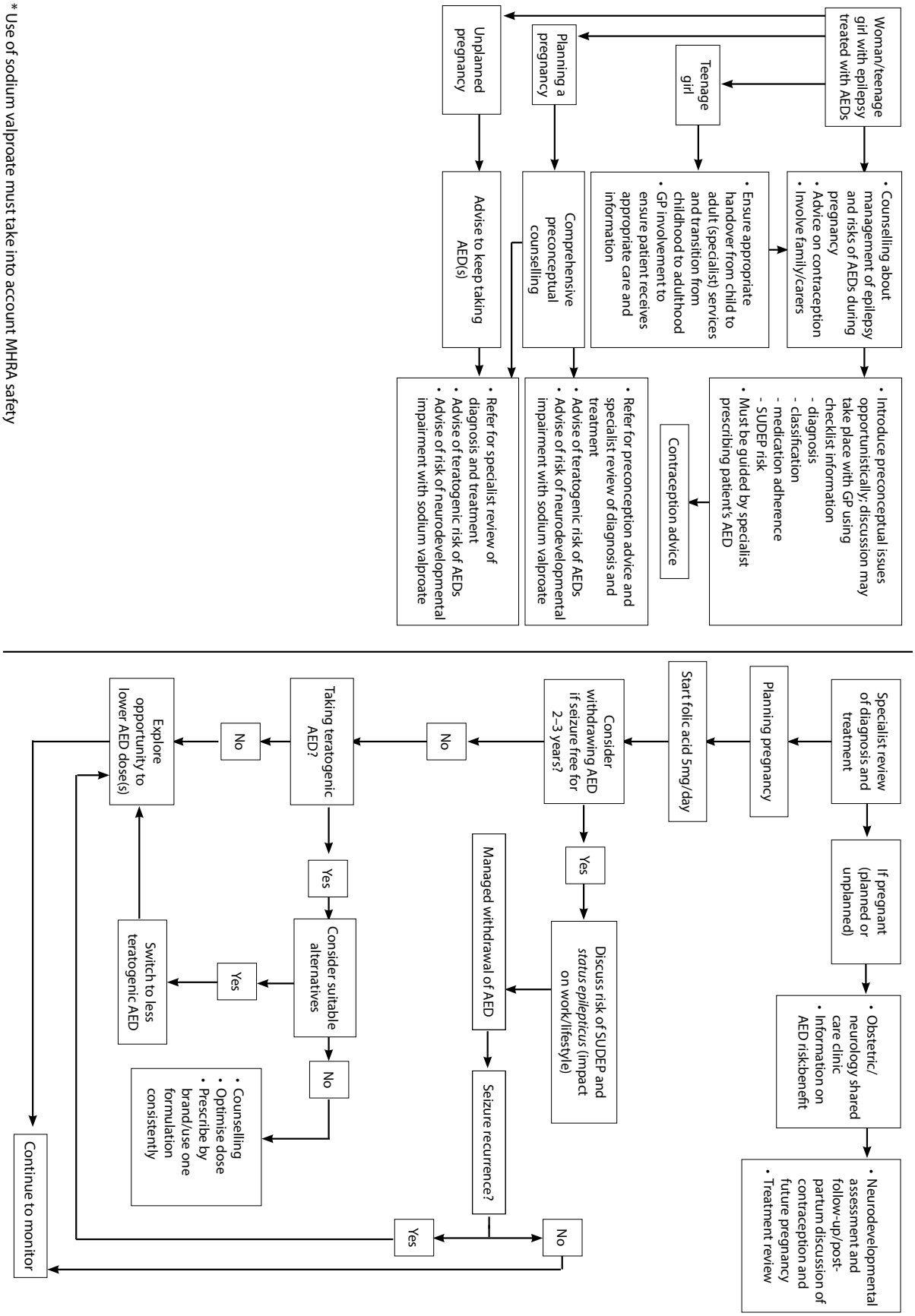
✓ When a woman with epilepsy presents in the early stages of labour, a low threshold for admission to the maternity unit should be adopted.

✓ During labour, one-to-one midwifery care should be given.

✓ Factors predisposing to increased risk of seizures in labour should be reduced as much as possible and there should be a low threshold for epidural anaesthesia.

D **The usual oral antiepileptic drug should be continued during labour and in the postnatal period. Every effort should be made to ensure that no doses are missed. In women with epilepsy who are unable to tolerate oral medication, the antiepileptic drug can be given by other routes.**

*Figure 2: Proposed management approach for women and teenage girls with epilepsy treated with antiepileptic drugs**



* Use of sodium valproate must take into account MHRA safety advice, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential and the conditions of the Pregnancy Prevention Programme.[454]

Reproduced with permission from: Epilepsy Expert Group - Clinical management algorithm for women and girls with epilepsy treated with antiepileptic drugs[248]

5.5.1 SEIZURES IN LABOUR

Approximately 3.5–5% of women with epilepsy will have a seizure during labour and birth.[284, 285] Intrapartum seizures are more common in those with antenatal seizures[284] and occur more frequently in women with primary generalised seizures than in women with focal-onset seizures.[301] 2+ 3

There are no clinical trials to inform choice of emergency treatment of intrapartum seizures for women with epilepsy. If the seizure persists, this should be managed as for *status epilepticus (see section 4.10)*.

D
- **Intrapartum generalised tonic-clonic seizures that are not due to eclampsia should be terminated as soon as possible.**
- **If the seizure persists, this should be managed as for *status epilepticus*.**

✓ Maternal airway and oxygenation should be maintained at all times.

✓ If there is doubt whether a seizure in labour is due to eclampsia or epilepsy, a slow intravenous bolus of 4 g magnesium sulphate over five minutes followed by 1 g/hour for 24 hours is recommended in addition to midazolam, lorazepam or diazepam.

✓ Following a generalised tonic-clonic seizure during labour (irrespective of aetiology) delivery should be expedited once the maternal condition is stable. Neonatal expertise should be available.

5.5.2 INDUCTION OF LABOUR

Induction of labour should be offered to women with epilepsy for standard obstetric indications. Epilepsy, in itself, is not an indication for induction of labour and there is no evidence to show that induction of labour is associated with improved pregnancy outcomes. It may, nevertheless, be reasonable to consider induction of labour in a woman with poorly controlled seizures at term.

✓ In women with epilepsy, induction of labour should be offered for standard obstetric indications.

5.5.3 CAESAREAN SECTION

Epilepsy alone is not an indication for Caesarean section and there is no evidence to show that Caesarean section is associated with improved pregnancy outcomes in women with epilepsy. Delivery by elective Caesarean section may, however, be appropriate for a woman with frequent tonic-clonic or prolonged focal seizures towards the end of pregnancy.

Evidence on whether or not women with epilepsy are at substantially increased risk (greater than two times expected) of delivery by Caesarean section is conflicting.[262, 282, 302] Higher rates have been found in women with active seizures,[285] and those taking AEDs.[251] 2++ 3

Further research on pregnancy and perinatal outcomes following induction of labour and Caesarean section for women with epilepsy is required

✓ A history of epilepsy alone is not an indication for delivery by Caesarean section. Elective Caesarean section should be considered if there have been frequent tonic-clonic or prolonged focal seizures during the third trimester of pregnancy in order to avoid adverse outcomes associated with intrapartum seizures.

5.5.4 OBSTETRIC HAEMORRHAGE

Evidence on whether or not women with epilepsy are at increased risk of bleeding complications is inconsistent. A systematic review demonstrated no increased risk,[251] but a large population-based study demonstrated an increased risk of postpartum haemorrhage in women with epilepsy compared to those without epilepsy, particularly for those taking AEDs (odds ratio (OR) 1.5, 95% CI 1.3 to 1.9).[303] 2++

Further research into postpartum haemorrhage rates in women with epilepsy is required. Outcome data could be incorporated into existing pregnancy registers.

5.6 FETAL, NEONATAL AND CHILDHOOD OUTCOMES

The effect of maternal epilepsy on fetal and infant outcomes is unclear and data from studies are inconsistent. These inconsistencies may be due to geographical factors and social differences between different populations, differences in the aetiology of epilepsies, and differences in the management of epilepsy and pregnancy.

5.6.1 RISKS TO THE FETUS FROM MATERNAL SEIZURES

The majority of women with epilepsy will have unchanged or improved seizure frequency during pregnancy *(see section 5.4.1)* although up to one third will experience an increase in seizure frequency.[287, 304] This increase may be due to a number of factors including changes in AED pharmacokinetics and poor adherence to treatment because of concerns about teratogenicity.[252] 3

The long term effect of maternal seizures on the fetus is not well established, although in theory the associated hypoxia and acidosis could adversely affect fetal outcomes, particularly if seizures are frequent and prolonged.

D **Pregnant women with epilepsy should be made aware of the risks of uncontrolled seizures both to themselves and to their developing fetus.**

5.6.2 RISKS TO THE FETUS ASSOCIATED WITH ANTIEPILEPTIC DRUGS

Epilepsy is common in women of childbearing age and exposure of the fetus to AEDs occurs in approximately 1 in 250 pregnancies.[206]

Women with epilepsy are more likely than women without epilepsy to give birth to children with congenital malformations (CMs).[256, 259, 260, 262, 263, 305, 306] Untreated epilepsy does not appear to be associated with an increased risk of CM,[307] but major and minor fetal malformations occur more commonly in infants exposed to AEDs during pregnancy.[252, 308-310] 2++ 2+ 3

The overall risk of major congenital malformation (MCM) in the general population is approximately 2%.[252, 311, 312] The risk increases in women taking a single AED *(see section 5.6.3)* or multiple AEDs *(see section 5.6.4)*. 2+

✓ A detailed assessment of fetal anatomy to detect fetal congenital abnormalities should be offered to all pregnant women with epilepsy at 18–20 weeks gestation.

5.6.3 RISKS TO THE FETUS ASSOCIATED WITH ANTIEPILEPTIC DRUG MONOTHERAPY

The reported rates of MCMs associated with different AED monotherapies vary from study to study and different methodological approaches make comparison between studies difficult. Rates are, however, consistently higher for sodium valproate than for other AEDs *(see Table 4)*.

Table 4: Absolute risk of major congenital malformation risks with AED monotherapy[313]

AED	MCM risk
***Sodium valproate**	11.3%[262] 10.7%[312] 8.9%[314] 7.5%[315] 6.3%[316] 6.2%[263]
***Carbamazepine**	5.2%[316] 4.6%[312] 3.3%[317] 3.0%[262] 2.2%[318]
Phenytoin	7.4%[312] 3.7%[318] 2.9%[316]
***Lamotrigine**	5.4%[319] 5.2%[316] 3.2%[318] 2.9%[312] 2.2%[320] 1.9%[262]
Gabapentin	4.1%[321]
Topiramate	4.8%[313] 4.3%[322] 3.1%[316]
Levetiracetam	0.7%[323] 0.0%[324]
*For lamotrigine, sodium valproate and carbamazepine montherapies, there is evidence to suggest that there is an increased risk of teratogenicity associated with an increased dose.[318, 325, 326]	

At present there is insufficient evidence on which to base advice about the teratogenic risks associated with vigabatrin, ethosuximide, tiagabine, pregabalin, zonisamide, rufinamide, lacosamide and perampanel monotherapy in pregnancy.

Sodium valproate

The teratogenic risk associated with sodium valproate is higher than with other AEDs both as mono- and polytherapy *(see section 5.6.4)*.[327] The teratogenic effect of sodium valproate is dose dependent and greatest for daily doses >1,100 mg.[325] High CM rates associated with prenatal sodium valproate exposure are more likely to be related to the total daily dose, rather than peak serum concentrations. Prescribing controlled release sodium valproate or administering it in multiple divided doses does not reduce the risk of congenital malformations.[314] 2+ 3

Safety advice from MHRA, issued in April 2018, on use of valproate medicines in women and girls of childbearing potential, states that valproate medicines must no longer be used in these groups unless there is no suitable alternative and the conditions of the Pregnancy Prevention Programme are met *(see section 5.2.0)*.[454]

D **Women with epilepsy should be informed that sodium valproate is associated with a higher rate of teratogenicity compared to other antiepileptic drugs.**

✓ Wherever possible sodium valproate should be avoided during pregnancy.

✓ For women of childbearing potential, particularly those women contemplating pregnancy, other antiepileptic drugs should be considered in preference to sodium valproate. However, sodium valproate might be the only effective antiepileptic drug for some women, and this should not preclude its use.

✓ Given the morbidity and mortality risks associated with seizures (including sudden unexpected death in epilepsy) no antiepileptic drug should be discontinued during pregnancy unless this has been discussed with an epilepsy specialist.

Specific congenital malformations

The most common MCMs associated with established AEDs are neural tube defects (sodium valproate 3%, carbamazepine 1%), cardiovascular defects, oral clefts and urinary tract defects.[256, 259, 262, 308, 328] Carbamazepine teratogenicity appears to be relatively specific to fetal spina bifida, although the risks are lower than with sodium valproate.[315] There is, however, conflicting evidence about this association.[281] In 2011, the US Food and Drug Administration issued a warning about the increased risk of orofacial clefts (lip and/or palate) associated with topiramate use in pregnancy,[329] although limited evidence is available to confirm or refute this association with studies arriving at different conclusions.[313, 322, 330] Lamotrigine monotherapy does not appear to be associated with an increased risk of isolated orofacial clefts relative to other CMs.[331] 2++ 2+ 3 4

Antiepileptic drug therapy in pregnancy also increases the risk of minor malformations including hypertelorism, epicanthic folds and digital hypoplasia.[309] Monotherapy with sodium valproate and carbamazepine, but not phenytoin, clonazepam, lamotrigine or gabapentin, has been shown to be associated with a significant reduction in neonatal head circumference but not microcephaly (>2 standard deviations below mean head circumference).[332] 2+ 3

Fetal anticonvulsant syndromes

Fetal anticonvulsant syndromes, comprising typical dysmorphic craniofacial appearances and a variety of musculoskeletal abnormalities, have been described as associated with AED treatment in pregnancy.[333-335] Although individual drugs have been associated with specific patterns, there is overlap, and genetic factors may influence susceptibility.[335, 336] 3 4

5.6.4 RISKS TO THE FETUS ASSOCIATED WITH ANTIEPILEPTIC DRUG POLYTHERAPY

Polytherapy carries a much higher risk of MCM than monotherapy *(see section 5.6.3)* at up to 24% in women taking four AEDs.[252, 308-310, 312] Studies of polytherapies including sodium valproate have reported MCM rates of: 2+ 3

- sodium valproate/lamotrigine polytherapy, 9.1%,[337] 9.6%,[318] 10.7%[320]
- sodium valproate/carbamazepine polytherapy, 8.8%,[318] 10.7%.[320]

Due to concerns about teratogenicity, safety advice issued by MHRA in April 2018 on use of valproate medicines in women and girls of childbearing potential, states that valproate medicines must no longer be used in these groups unless there is no suitable alternative and the conditions of the Pregnancy Prevention Programme are met *(see section 5.2.0)*.[454]

Lamotrigine polytherapy regimens that do not contain sodium valproate are associated with a low rate of teratogenicity (2.8%,[320] 2.9%[337]). 3

AED polytherapy is more likely to result in microcephaly although evidence suggests this does not impact on childhood neurodevelopmental outcomes at 3 years of age.[338]

D **Women with epilepsy should be informed that antiepileptic drug polytherapy regimens including sodium valproate are associated with higher rates of congenital malformations compared to regimens not including sodium valproate.**

✓ Whenever possible, antiepileptic drug polytherapy regimens including sodium valproate should be avoided in women of childbearing potential because of the increased risk of congenital malformations.

5.6.5 RECURRENCE RISK OF CONGENITAL MALFORMATION

The risk of CM in women with epilepsy without a history of CM is 9.8%. This risk increases to 16.8–35.7% if there is history in a previous child, and 50% if two previous children have been affected. There is a trend for risks to be higher for women exposed to sodium valproate and topiramate, but not other monotherapies. Risks are also higher for polytherapy regimens where the AED dose had been increased after the first pregnancy.[339, 340] 3

✓ Any woman with epilepsy who has given birth to a child with a congenital malformation while taking an antiepileptic drug should be offered review by an obstetrician and an epilepsy specialist before any future pregnancy.

5.6.6 PERINATAL OUTCOMES

The majority of women with epilepsy will deliver a healthy baby at term. There is, however, some evidence that epilepsy may be associated with adverse perinatal outcomes, particularly for women taking AEDs.

Evidence to determine whether or not epilepsy is associated with an increased risk of stillbirth and neonatal death is limited, although a systematic review concluded that there is probably no substantially increased risk of perinatal mortality in the offspring of women with epilepsy.[341] A large Danish study found no overall association between the use of AEDs during pregnancy and spontaneous miscarriage or stillbirth, although the statistical precision of the latter was low.[342]

In women with epilepsy taking AEDs, the risk of having a small for gestational age (SGA) infant is double the expected rate in the general obstetric population, but the impact of different AEDs is not known.[282, 341, 343] There is insufficient evidence to support the use of routine ultrasound scanning in the third trimester of pregnancy to detect a SGA fetus, however, if a SGA fetus is suspected clinically, an ultrasound scan should be performed to assess fetal biometry. If an SGA fetus is identified in a women with epilepsy, AED use should be considered as a potential aetiological factor.[341] 2^{++}

The offspring of women with epilepsy taking AEDs are twice as likely as expected to have a 1 minute Apgar score of <7.[282 341]

There is insufficient evidence to conclude whether or not the offspring of women with epilepsy are at increased risk of respiratory distress, intrauterine growth restriction and neontatal intensive care unit admission.[341]

Further research is required to provide definitive information on perinatal outcomes for women with epilepsy taking antiepileptic drugs, particularly perinatal outcomes for specific antiepileptic drugs.

C **Women with epilepsy should be reassured that antiepileptic drugs do not increase the risk of spontaneous miscarriage and stillbirth**

5.6.7 CHILDHOOD OUTCOMES

There is no evidence that untreated maternal epilepsy is associated with impaired cognitive development in offspring.[341, 344] 2++ 2+

There is, however, evidence to suggest that the offspring of women with epilepsy receiving AEDs are at increased risk of poor cognitive outcome although evidence about which AEDs increase the risk is inconsistent. Some studies suggest that carbamazepine monotherapy does not increase the risk of poor cognitive outcomes compared to unexposed controls but that sodium valproate, phenytoin and phenobarbital monotherapy are associated with an increased risk.[265, 341, 345] A prospective multicentre study assessing intelligence quotient (IQ) at six years of age in 224 children born to women taking carbamazepine, lamotrigine, phenytoin or sodium valproate monotherapy, reported that IQ was significantly lower after exposure to sodium valproate (with a dose-dependent relationship) than to the other AEDs, with verbal and memory abilities being particular problems *(see section 5.2.1)*.[265] 2++

Other adverse outcomes that have been linked to AEDs include childhood verbal language impairment associated with fetal exposure to sodium valproate,[346] impaired neurodevelopment in infants exposed to sodium valproate or carbamazepine but not lamotrigine,[347] and autism spectrum disorder and childhood autism in children exposed to sodium valproate prenatally.[345] There is, however, insufficient evidence to make recommendations about treatment with any specific AED or combination of AEDs. 2++ 3

Due to concerns about teratogenicity, safety advice issued by MHRA in April 2018 on use of valproate medicines in women and girls of childbearing potential, states that valproate medicines must no longer be used in these groups unless there is no suitable alternative and the conditions of the Pregnancy Prevention Programme are met *(see section 5.2.0)*.[454]

✓ For women with epilepsy who require treatment with antiepileptic drugs during pregnancy the relative risks of seizures and risks of fetal, neonatal and childhood problems should be discussed.

✓ Consideration may be given to withdrawal of antiepileptic drugs prior to conception if circumstances are favourable. The decision should only be made if the epilepsy is in remission, the risk of recurrent seizures is low and the woman is aware of the consequences of recurrent seizures.

✓ Wherever possible, a woman should conceive on the lowest effective dose of one AED appropriate for her epilepsy syndrome. If she has good seizure control and presents already pregnant, there is probably little to be gained by altering her AEDs

5.7 POSTPARTUM ADVICE FOR MOTHERS

Following delivery, physiological changes associated with pregnancy gradually remit and blood levels of AEDs may rise. If AED dosing was increased in pregnancy, this may lead to toxicity postpartum and dosing may need to be reduced at this time.

Caring for a young baby is often associated with fatigue and sleep deprivation, both of which can provoke seizures. Evidence suggests that the first three days after delivery are associated with a higher risk of seizures.[286] Although injuries to infants from maternal seizures are thought to be uncommon, babies of women with epilepsy, especially mothers with myoclonic epilepsies, are at risk. Bathing infants is potentially hazardous if the mother has seizures associated with loss of awareness. 3

The postnatal check provides an opportunity to examine the infant for any abnormality.

✓ All pregnant women with epilepsy should be encouraged to plan ahead before the birth of their child.

✓ Where seizure control is poor and/or social factors have the potential to affect outcomes adversely, a care management plan should be considered before delivery. It should be ensured that health professionals, both in the community and in secondary care, are aware of the potential risks to the woman and her baby.

✓ Advice should be given to new parents/child carers on safety, particularly in relation to breastfeeding and caring for the child.

✓ After the birth a review of the mother's AED therapy should be undertaken.

✓ Advice regarding contraception, the need for planning future pregnancies, folic acid requirements and risks associated with AEDs in pregnancy should be offered at the postnatal visit.

✓ Extra support should be available to mothers who have a physical or learning disability.

5.7.1 POSTPARTUM CONTRACEPTION

Postpartum contraceptive advice helps women to plan future pregnancies,[348] and reliable contraception should be discussed early in the postpartum period *(see section 5.1)*. Interpregnancy intervals of less than six months have been associated with an increased risk of negative perinatal outcomes.[349] Short interpregnancy intervals also increase the risks to maternal health,[350] therefore, delaying future pregnancies may be beneficial in terms of health. 4

✓ As with all women following delivery, timely advice should be given to those with epilepsy regarding contraception.

✓ Progesterone-only oral contraception, which is often the contraceptive method of choice in women who are breastfeeding, is contraindicated postpartum in women with epilepsy taking hepatic enzyme-inducing AEDs as these increase progesterone metabolism.

5.8 ADVICE ABOUT BREASTFEEDING

AED plasma concentrations in infants who are breastfed are generally lower than in utero, provided the infant is healthy and born close to term.[290, 296, 351-353] Although AEDs pass into breast milk at varying levels there is no consistent evidence to show accumulation of any AED in breastfed newborn of women with epilepsy. Data suggest probable penetration into breast milk of primidone and levetiracetam in amounts that may be clinically important, possible penetration of gabapentin, lamotrigine and topiramate, and probably no penetration, in clinically important amounts, of sodium valproate, phenobarbital, phenytoin and carbamazepine.[266] Breastfeeding and subsequent weaning usually allow for a gradual withdrawal with usually no adverse sequelae for the infant.[354-356] 3

Accumulation of AEDs may occur due to immature mechanisms for drug elimination and, therefore, close monitoring is recommended, particulaly if the baby is preterm, jaundiced, or if the mother started taking AEDs late in pregnancy or after delivery.[357] There may also be a risk of toxicity in the breastfed infant if the mother is on a high dose of AEDs or polytherapy. Parents should be made aware of signs of toxicity in the infant and encouraged to seek medical advice if these occur.[357]

✓ All mothers should be encouraged to breastfeed and receive support from their health visitor, midwife and GP.

D **Parents should be made aware of signs of toxicity in infants of breastfeeding women taking antiepileptic drugs. The possibility of sedation should be considered in infants of mothers taking high dose antiepileptic drugs, polytherapy, or regimens including primidone, levetiracetam, gabapentin, lamotrigine and topiramate.**

5.9 MENOPAUSE AND EPILEPSY

Information about the effects of the menopause on epilepsy is limited. In one study in 68 women with epilepsy, menopause occurred 3–4 years earlier in patients with more than one seizure a month independent of other factors.[358] There is some evidence to suggest that seizure frequency may alter in perimenopausal women, perhaps due to changing oestrogen concentrations,[359] and some women experience an increase in seizure frequency at this time.[360, 361] Bone disease associated with epilepsy becomes an important issue after the menopause *(see section 4.6.4)*.[145, 362]

1+
2+
3

Data regarding hormone replacement therapy (HRT) and seizures are conflicting. HRT may improve seizure control in those who previously experienced catamenial epilepsy (seizures with menstruation) but could be associated with increased seizure frequency in others.[361, 363] One small study found HRT containing the combination of conjugated equine oestrogens and medroxyprogesterone acetate was associated with worsening seizures and a reduction in lamotrigine concentrations.[364]

1++
2+
3

Enzyme-inducing AEDs *(see Table 3)* reduce the efficacy of standard doses of HRT.[213]

Further research on the menopause in women with epilepsy is required.

D **Women should be aware that their seizure pattern may change around the menopause.**

D **Hormone replacement therapy should be prescribed for the same indications as in women who do not have epilepsy.**

6 Psychiatric comorbidity

Psychiatric comorbidities in people with epilepsy are common but may go undiagnosed and untreated. Several large epidemiological studies have reported increased rates of psychiatric comorbidity in people with epilepsy compared to the general population,[365, 366] and compared to patients with other chronic conditions such as asthma, with one reporting a rate of depression of 36.5% for people with epilepsy, compared to 27.8% for patients with chronic asthma and 11.6% in the control group.[367]

Major depression is the main psychiatric comorbidity in people with epilepsy with rates of 24% recorded.[368] This represents a significant additional burden to patients, their families and the healthcare system with people with depression more likely to access healthcare resources.[369] One study showed that up to 38% of patients with a lifetime history of major depression had never received treatment and another showed a 10-fold increase in detection of depression in their seizure clinic after the introduction of regular screening with the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) *(see section 6.1.1)*.[370] Up to a fifth of people with epilepsy also have an anxiety disorder,[371] resulting in reduced measures of self efficacy and quality of life.[372, 373]

Suicide rates in people with epilepsy three times higher than those seen in the general population have been reported,[374] with one study reporting that suicide was 13 times more common in patients with epilepsy who also had a comorbid psychiatric condition.[374] This finding is supported by a large hospital-based study of over 9,000 people with epilepsy that reported a Standardised Mortality Ratio (SMR) in people with epilepsy of 3.5 (95% CI 2.6 to 4.6).[375]

Psychosis in people with epilepsy can present as a chronic condition or be episodic in nature, having a direct relationship to seizures. A recent systematic review established that as many as 6% of patients will have a comorbid psychotic illness, although this can rise to 7% in people with temporal lobe epilepsy.[376] This study supports the findings of an earlier large epidemiological study.[377] The additional burden of episodic psychosis cannot be underestimated with patients suffering sadness, embarrassment and confusion about the events which may have taken place during the psychotic episode.

There remains an innate tension between the gold standard of assessment with structured psychiatric diagnostic interviews conducted by appropriately trained mental health professionals and the need for healthcare professionals to have access to screening tools which are valid, reliable and easily administered in busy clinical areas. Identification of patients with epilepsy and comorbid psychiatric conditions is, however, important and suitable screening tools should be deployed in all epilepsy clinics.[378]

6.1 SCREENING

Screening tools to establish the presence of depression, anxiety and suicidality in people with epilepsy are, in general, the same as those for the general population.

Screening tools for healthcare professionals need to be easily administered and sensitive to treatment effects in order to measure psychiatric comorbidity in people with epilepsy.

6.1.1 DEPRESSION

The NDDI-E is a self-rating tool with six questions and easily understood scoring specifically designed for, trialled and validated in people with epilepsy. It does not appear to be affected by drug adverse effects, unlike other measures.[378]

Other general screening tools include the Patient Health Questionnaire 2 (PHQ-2) (two questions),[379] the Hospital Anxiety and Depression Scale Depression subscale (HADS-D), the Beck's Depression Inventory (BDI-II) (21 questions), the Centre for Epidemiological Studies Depression scale (20 questions) and the Distress Thermometer, a single-item visual analogue scale designed to measure subjective distress in the past week.[380]

Direct comparison of the NDDI-E with the PHQ-2 showed little difference in sensitivity and specificity at detecting depression.[366] Further comparison between NDDI-E and HADS-D has shown that the NDDI-E may be superior when eliciting the presence of Mini International Neuropsychiatric Interview defined moderate to high suicide risk compared with the HADS-D scale >8.[368]

Comparison of the Distress Thermometer, the NDDI-E, HADS-D, and BDI-II using the World Health Organisation (WHO) Major Depression Inventory to identify depression as defined by DSM-IV and ICD-10 suggests that they are similar in their ability to rule out the presence of depression. There was no difference in diagnostic accuracy and no evidence that one is superior to another, but in the interests of brevity either the NDDI-E or HADS-D should be considered. In patients where literacy cannot be assumed, visual analogue scales like the Distress Thermometer should be considered.[381] 3

6.1.2 ANXIETY

No screening tools designed specifically to measure anxiety in patients with epilepsy were found. In the absence of such tools, the HADS and General Anxiety Disorder 7 can be considered although these have not been validated in people with epilepsy.[371]

6.1.3 PSYCHOSIS

No tools were found for screening psychosis in patients with epilepsy.

6.1.4 SUICIDALITY

Given that suicidality is significantly raised in people with epilepsy, screening tools are needed that can identify this risk. The NDDI-E has been shown to have a higher sensitivity than the HADS-D at identifying suicidal ideation (81% *v* 43%), although its specificity was lower (66 % *v* 91%); it should, therefore, be considered as superior to the HADS-D as a screening measure for severe depression and suicidal ideation.[368] 3

6.1.5 LEARNING DISABILITY

No screening tools specifically for use in patients with a learning disability and epilepsy were found. As rates of psychiatric comorbidity in patients with a learning disability are high,[382] and assessment in this population requires specific instruments, the Glasgow Anxiety Scale and the Glasgow Depression Scale for People with Learning Disability (GDS-LD),[383, 384] both designed for use with those with mild to moderate learning disability, could be considered, although these are not specifically validated in people with epilepsy.

6.1.6 FUTURE RESEARCH

Future research into the effectiveness of screening for psychiatric comorbidity in patients with epilepsy should include broad-ranging general population studies, to reduce the risk of heterogeneity, and these should include the full spectrum of people with epilepsy. Standard definitions and measures should be employed. The gold standard of structured psychiatric diagnostic interviews in studies evaluating screening tools is required to fully investigate their sensitivity and specificity for detecting the presence of the full range of psychiatric comorbidities in people with epilepsy.[371]

Future studies should be mindful of the specific cognitive deficits people with epilepsy experience, such as reduced concentration, increased memory difficulties and fatigue alongside disturbance in sleep, as these overlap with many somatic symptoms of depression and could act as confounders.

D **Screening for depression and suicidality should be considered in all patients with epilepsy.**

D **The NDDI-E, HADS-D, BDI-II or PHQ-2 can all be used to screen for depression in adults with depression and epilepsy. The NDDI-E may be superior for detecting severe depression and suicidal ideation.**

✓ When screening identifies the presence of possible psychiatric comorbidity, people with epilepsy should be referred to an appropriately trained mental healthcare professional for further assessment and, where relevant, treatment.

✓ Screening tools used by non-mental healthcare professionals should be brief, easily administered and easily understood.

✓ Although not specifically validated for use in epilepsy, consideration should be given to using screening tools such as the Glasgow Anxiety Scale or the Glasgow Depression Scale for People with Learning Disability in patients with intellectual disability.

✓ Assessment of anxiety and depression should, where relevant, be considered as part of a multidisciplinary approach to patient-centred care.

6.2 TREATMENT OPTIONS

Evidence for treatment options for the management of psychiatric comorbidity in people with epilepsy is limited to the management of depression and anxiety, the prevalence of both of which are high in patients with epilepsy *(see section 6)*,[371] often underdiagnosed and undertreated partly due to healthcare professionals' concerns regarding possible negative effects of psychotropic medication.[385] 2+ 3

Comorbid depression in people with epilepsy is associated with poor seizure control,[386,387,388] increased healthcare costs,[369] and with a greater impact on quality of life than the number of prescribed antiepileptic drugs or seizure frequency.[389, 390]

✓ Treatment of anxiety and depression should, where relevant, be considered as part of a multidisciplinary approach to patient-centred care.

6.2.1 NON-PHARMACOLOGICAL TREATMENT

Two systematic reviews provide some evidence of benefit for cognitive behavior therapy (CBT) in the treatment of depression in people with epilepsy, but conflicting results and methodological limitations of the included studies, and the small numbers of patients included in the trials, limit the conclusions that can be drawn.[159, 385] One review reported benefit from CBT in three out of six RCTs, with benefit confined to RCTs where the CBT was specifically tailored to improve depression rather than seizure control.[385] There is, however, insufficient evidence on which to base a recommendation. 1++ 2++

6.2.2 PSYCHOTROPIC MEDICATION

No convincing evidence was identified that showed the relative efficacy of antidepressants for the treatment of depression in people with epilepsy.[391, 392] 2-

Antidepressants, in particular selective serotonin reuptake inhibitors, appear to be safe to use in patients with epilepsy and comorbid depression.[391, 393-395] 2+ 3

Antidepressants are effective in the treatment of depression in people with chronic illness including neurological disorders,[396] and it is reasonable to extrapolate these findings to patients with epilepsy as the issues of comorbidity, confounding and variable disease course are similar. Studies looking specifically at the treatment of depression in patients with epilepsy are limited to observational studies, often of low quality and in highly selected populations in single, generally tertiary, centres and with varying definitions and degrees of depression, making comparison difficult. 1+

A recent review of the possible association between the use of AEDs and suicide concluded that there was no clear evidence to confirm or rule out an association because of heterogeneity in the included studies at the clinical and the methodological level. Most of the studies considered the effect of AEDs as a single class effect and this assumption may need to be revisited in light of the different effects of the different AEDs on mood *(see section 4.6.5)*.[397] 2++

D **Treatment with antidepressants should be considered in patients with epilepsy and comorbid depression.**

6.2.3 COGNITIVE REHABILITATION

Cognitive problems in people with epilepsy commonly involve learning, memory and executive function (impulsivity, planning and organisation, and multitasking). In one study of 700 patients with epilepsy, 54% reported memory problems,[398] although it is not known how this compares with the general adult population. Epilepsy-specific memory deficits including 'accelerated forgetting', remote memory impairments and transient epileptic amnesia have also been reported.[399, 400] 2+ 3

Memory and attention problems can be identified using cognitive screening tools such as the Addenbrook's Cognitive Assessment (third version), although these are not specific to patients with epilepsy.[211] When more in-depth neuropsychological assessment is required, this should be provided by a suitably qualified clinical psychologist specialising in neuropsychology. There is no agreement on which measures to use to investigate the effects of cognitive rehabilitation in epilepsy.

Cognitive rehabilitation through compensation strategy training (where people are taught to use aids, prompts and methods to help them augment their cognitive abilities) and the retraining method (which aims to develop more cognitive facility and capacity by viewing memory as a muscle which can be built up and improved) with some form of support or psychoeducation regarding the nature of memory problems implicit in the rehabilitation, have been investigated. A comparison of the effects of a cognitive retraining method with a compensatory training method to treat attention problems in a small group of people with focal seizures receiving monotherapy (n=44 completing follow-up assessments), reported improvements in self-reported quality of life measures in both treatment groups, compared to the control group, at six months follow up. The compensation method was the more effective of the two approaches, particularly to those with less education.[401] 1-

Cognitive rehabilitation may also benefit some patients undergoing temporal lobe resection. One study in 57 patients reported that patients with right temporal lobe epilepsy with verbal memory problems appeared to respond well to cognitive rehabilitation, whereas effects were limited for those with left temporal lobe epilepsy. Further research is needed on what types of training help which patients and when it should be offered.[402] 2+

Cognition in epilepsy may be helped by cognitive rehabilitation and there are no adverse effects of the treatment. There is, however, currently insufficient evidence on which to base a recommendation.

✓ Centres and researchers studying cognition in epilepsy, and the effectiveness of cognitive rehabilitation on memory and other cognitive deficits in epilepsy, should use comparable measures and assessments.

✓ Cognitive rehabilitation and psychoeducation should be part of multidisciplinary care for people with epilepsy.

✓ Memory problems can be distressing and/or disabling and should, in the first instance, be identified by a cognitive screen. There should be access to specialist neuropsychological opinion and advice, as deemed appropriate by the multidisciplinary team.

7 Sleep

Sleep and epilepsy have reciprocal interactions: on the one hand, sleep (and sleep deprivation) can be a trigger for seizure onset in some forms of epilepsy; on the other, epileptic seizures and antiepileptic drugs disrupt normal sleep, contributing to the morbidity of epilepsy.[403] Distinguishing non-epileptic sleep disorders (such as parasomnias) from seizures may also present particular difficulties and may require specialist investigation *(see section 3.4.4)*.[403]

Other relationships between sleep and epilepsy have gained attention in recent years, notably the possible interaction between obstructive sleep apnoea and epilepsy, and the importance of nocturnal seizures in SUDEP.

7.1 SLEEP DEPRIVATION AND SLEEP HYGIENE

Observational data suggest that sleep deprivation can precipitate seizures in people with epilepsy, as well as activating underlying EEG abnormalities.[404] This effect is most marked in the genetic epilepsy syndromes, and is less clear in focal epilepsies.[405]

✓ People with epilepsy, particularly those with a genetic epilepsy, should be advised that sleep deprivation may precipitate seizures, and be provided with advice to obtain sufficient sleep with a regular sleep/wake pattern.

7.2 OBSTRUCTIVE SLEEP APNOEA AND EPILEPSY

It has been suggested that people with treatment-resistant epilepsy are at increased risk of developing obstructive sleep apnoea (OSA),[405, 406] and that treatment of OSA with continuous positive airway pressure (CPAP) may improve seizure frequency.[407, 408] 2-

OSA is characterized by impaired breathing during sleep, and affected individuals usually report excessive daytime sleepiness, loud snoring, and often witnessed breathing pauses. It is known to cause daytime fatigue, sleepiness and cognitive problems and it is possible that recognition and timely management of OSA may improve seizure control, cognitive function and quality of life in people with treatment-resistant epilepsy.

Definitive evidence of either an increased prevalence of OSA in people with epilepsy, or a beneficial effect on seizures from CPAP treatment in patients with OSA, is lacking and there is, therefore, insufficient evidence to recommend routine investigation for OSA in people with epilepsy in the absence of a clinically suggestive history.

✓ Healthcare professionals should enquire about the cardinal features of obstructive sleep apnoea in individuals with treatment-resistant epilepsy, and refer them to specialist sleep services for further assessment if obstructive sleep apnoea is clinically suspected.

7.3 SUDDEN UNEXPECTED DEATH IN EPILEPSY AND SLEEP

Sudden unexpected death in epilepsy is discussed in detail in section 8. It is, however, highlighted here as observational data suggest that individuals with frequent nocturnal convulsive seizures are at increased risk of SUDEP, with around 60% of cases of SUDEP occurring during sleep.[409]

✓ Individuals with nocturnal seizures should be counselled about the increased risk of sudden unexpected death in epilepsy as part of counselling about the risks of epilepsy and preventative measures (particularly adherence with antiepileptic drug treatment).

8 Mortality

Studies from around the world report premature death in adults with epilepsy compared to the general population, with standardised mortality ratios of 3–5 having been reported.[375, 410-412] The majority of these deaths occur in people under 55 years of age.[375, 413] A total population study from Scandanavia reported a median age of death of 34.5 years (interquartile range 21–44 years) with an adjusted OR of 11.0 for premature death in people with epilepsy compared with an unaffected sibling and an age-matched control.[413]

Premature death in epilepsy has a wide variety of causes including alcohol misuse (SMR 24.6, 96% CI 21.0 to 28.6),[375] drowning (OR 7.7, 95% CI 4.7 to 12.7), falls (OR 8.8, 95% CI 5.3 to 13.7), drug poisoning (OR 5.1, 95% CI 3.9 to 6.5) and motor vehicle accidents (OR 1.4, 95% CI 1.1 to 1.8).[413]

Another significant cause of premature mortality is suicide. A population based study of suicide in epilepsy reported a suicide rate in people with epilepsy three times higher than in the general population, with rates increased further in people with epilepsy who had a comorbid psychiatric condition *(see section 6)*.[374]

8.1 SUDDEN UNEXPECTED DEATH IN EPILEPSY

Of all the causes of premature mortality in people with epilepsy, SUDEP commands the most attention because of its sudden appearance and devastating aftermath. SUDEP is defined as sudden, unexpected, unwitnessed, non-traumatic, non-drowning death of a person with epilepsy, with or without a seizure, excluding documented *status epilepticus*, and in whom post mortem examination does not reveal a structural or toxicological cause of death.[414] The definition is descriptive, providing no insight into the possible causes of the phenomenon.

The reported incidence of SUDEP depends on the populations studied and the study methodology.[415, 416] Community-based studies in unselected cohorts of incident cases of epilepsy have the lowest risk of bias and give incidences of between 0.09 and 0.35/1,000 patient years.[415] Studies in prevalent populations give incidences of between 0.9 and 2.3/1,000 patient years,[415] while estimates in patients awaiting epilepsy surgery are higher at 6.3 to 9.3/1,000 patient years.[417, 418]

8.1.1 RISK FACTORS

Seizure type and frequency

Generalised tonic-clonic seizures (GTCS) are the principal risk factor for SUDEP, with studies demonstrating increased risk in individuals who sustained frequent GTCS.[419 420-423] A meta-analysis of 112 RCTs provides further evidence for the role of GTCS, reporting fewer deaths from SUDEP in the active treatment group.[424] Eye-witness reports and coroners studies also confirm that SUDEP is a seizure related phenomenon.[425-427] 1++ 1+ 2+ 3

There is some evidence from direct observation of SUDEP in video-EEG units and from case reports that SUDEP is more likely to occur during GTCS sustained in sleep.[425-427] 3

Further evidence for seizure as the principal risk factor is evidenced by the observation that patients who undergo successful epilepsy surgery, compared to those whose seizures continue, have SMRs similar to the background population.[428]

Early identification of treatment-resistant epilepsy (*see section 4.3)* and referral for assessment for epilepsy surgery *(see section 4.9)* to reduce seizure frequency may reduce incidence of SUDEP.

Antiepileptic drug treatment

There is no convincing evidence that SUDEP is caused by any single or combination of AEDs.[423, 426, 429] 2++ 3

Adherence

A large study of healthcare providers' databases in the USA reported an association between poor adherence and increased mortality.[430] Post mortem studies, usually involving small numbers of individuals, have reported subtherapeutic AED levels in some cases of SUDEP suggesting poor adherence to AED treatment.[431, 432] One study using post mortem hair analysis demonstated that discontinuation of AED treatment by patients appeared to increase the risk of SUDEP.[433] 3

Other risk factors

Early age of onset of epilepsy, AED polytherapy, concomitant psychotropic medication, and sleeping alone have been reported as risk factors for SUDEP.[416, 434, 435] These findings, however, are not consistent. One study, for example, showed that the association with AED polytherapy disappeared when GTCS frequency was taken into account.[423] 2^{++} 2^{+} 4

B **Healthcare professionals and patients should aim for complete seizure freedom to reduce the risk of sudden unexpected death in epilepsy.**

D **Adherence to the prescribed antiepileptic drug regime should be strongly encouraged and the patient asked to report any adverse effects that might compromise adherence in order to reduce the risk of increased mortality and morbidity.**

✓ Patients with active seizures, ie who have sustained seizures, and in particular generalised tonic-clonic seizures, in the past year, should be assessed by a specialist physician and epilepsy nurse specialist.

✓ The apparent increase in SUDEP in people with frequent nocturnal seizures should be highlighted to patients and nocturnal supervision could be considered.

✓
- Patients admitted to video-EEG units who will have their antiepileptic drugs reduced must be warned of the risk of SUDEP, although the risk is low.
- It is desirable that video-EEG units should monitor oxygen saturation levels as well as ECG and EEG.
- Video-EEG units must have adequate staff levels to respond immediately should the patient become apnoic or exhibit a significant cardiac arrhythmia.

8.1.2 MECHANISMS OF SUDEP

The mechanisms underlying SUDEP are not yet well understood,[435] and until they are, definitive advice about the role of seizure alarm systems, lattice pillows and avoiding the prone position during sleep, cannot be given.

One study reporting 16 directly observed cases of SUDEP (14 of which occurred at night) observed worldwide in video-EEG units reported that deaths occurred after a GTCS usually during sleep.[427] The immediate postictal phase was accompanied by rapid breathing, bradycardia or tachycardia, followed by terminal apnoea and asystole. The authors concluded that SUDEP occurs after GTCS because of a severe central disruption of cardiac and respiratory function. 3

Discussion of this and other proposed mechanisms for SUDEP is beyond the scope of this guideline.

8.1.3 COUNSELLING PATIENTS ABOUT THE RISKS OF SUDEP

A study of patients with epilepsy in the 16–30 age group suggested that the majority want information about SUDEP and that they prefer to receive this information face-to-face in the clinic rather than by leaflet. SUDEP disclosure may cause initial anxiety but there is no evidence that this is long lasting. There is no compelling evidence that knowledge of SUDEP improves adherence to treatment.[436, 437] 3

D **Counselling about the risks of sudden unexpected death in epilepsy should be considered for patients with epilepsy at an appropriate time for the patient and by an appropriate healthcare professional** (consultant neurologist, physician with an interest in epilepsy, specialist registrar, or epilepsy nurse specialist).

9 Models of care

The care of people with epilepsy is provided in primary (principally general practice-based), and secondary and tertiary (hospital-based) settings. Although there is no single accepted model of care for patients with epilepsy, co-ordination of care between these two settings and the involvement of epilepsy specialists from a range of disciplines is likely to result in the best overall care for the patient.

A survey of patients' perspectives on services for epilepsy reported that, "...most people with epilepsy (67.6%) would prefer their care to be community based, especially older patients and patients with mild epilepsy".[438] A further study also showed that, "...61% of patients would prefer their care to be shared between primary and secondary services".[439] 3

9.1 MODELS OF PRIMARY CARE FOR EPILEPSY

The primary-care needs of patients with epilepsy were well stated in a UK epilepsy needs document including the suggestion of an annual structured review, as was recommended for other chronic diseases such as asthma and diabetes.[440] Implementation of such management in primary care would be facilitated by the deployment of specialist epilepsy nurses, who can liaise between primary care and hospital care, and promote a shared care model.[438] 3

Primary-care professionals are gatekeepers to secondary-care access and co-operative evidence-based care shared between epilepsy-care providers is likely to enhance patient care. Patients with epilepsy who are seizure free on therapy and discharged from hospital review still have significant healthcare needs and require regular structured review in primary care to have these needs met.

A prospective audit to measure unmet clinical needs in 388 patients receiving treatment for epilepsy found a significant increase in the annual review rate and documentation of seizure frequency following introduction of the Quality Outcomes Framework GP contract for epilepsy in 2004 (now retired), but also showed that 48% of the 62 patients with poor control were not receiving shared care.[441] 3

Patients with suspected first seizure or epilepsy should be referred to a specialist in epilepsy and should be advised to take an eyewitness (to the attack) or contact details of someone who witnessed the attack to their consultation *(see sections 3.1 and 3.3)*.[442] 4

9.1.1 REGULAR STRUCTURED REVIEW

Regular structured review in primary care is an opportunity to ensure optimum management of patients with epilepsy and should be conducted by a healthcare professional who has "...attended an epilepsy training course in the past five years, or can demonstrate equivalent experience from continuing professional development".[442] In the view of the guideline development group, the review should be conducted annually and include questions about: 4

- seizure frequency
- date of last seizure
- focal seizures where appropriate
- AED dose
- AED adherence
- AED adverse effects
- coexistent low mood or depression
- driving status
- alcohol intake.

Seizure frequency and the date of a patient's last seizure reflect the degree of seizure control. Where seizures persist despite AED treatment, factors relating to poor control including incorrect diagnosis of epilepsy, inappropriate choice of AED for the epilepsy syndrome, and poor adherence to prescribed AEDs, should be

explored and referral to an epilepsy specialist considered *(see section 3 and section 4.3*). Seizures are also a risk factor for SUDEP and the goal should be seizure freedom *(see section 8)*.

Women of childbearing potential who are taking AEDs require specific information about contraception, conception and pregnancy and may require specialist review, in secondary care, of their diagnosis and treatment, prior to conception *(see section 5)*.

Adverse effects of AED treatment are common and sometimes serious *(see section 4.6)* and may contribute to poor adherence and poor control *(see section 4.3)*. It is therefore important to give the patient the opportunity to discuss these at their regular review.

The management of people with a learning disability and epilepsy is covered in section 4.15.

High rates of psychiatric comorbidity and increased risk of suicide compared to the general population have been reported in people with epilepsy along with quality of life issues relating to the epilepsy *(see section 6)*. Regular structured review in primary care provides an opportunity to identify such problems and provide patients with help and support where appropriate.

Epileptic attacks are the most frequent medical cause of collapse at the wheel and therefore have important implications for fitness to drive.[154] There is also some evidence that patients with seizure-free intervals of 12 months or more have substantially reduced odds of car accidents compared to patients with shorter seizure-free intervals.[443] This reinforces the need to attain good seizure control and to discuss with the patient the possible implications of driving with poorly-controlled seizures. Current guidance is that patients referred following a suspected first seizure or new epilepsy should be advised not to drive until they have seen an epilepsy specialist,[154, 442] and patients with established epilepsy who have had a seizure in the last year should be informed of current DVLA regulations.[154]

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4

Antiepileptic drug use is associated with a higher risk of clinical fracture and patients with epilepsy taking AEDs should therefore be given diet and lifestyle advice to reduce osteoporosis risk *(see section 4.6.4)*.

Provoked seizures may be related to intake or withdrawal of certain drugs or alcohol *(see sections 4.5 and 4.12)* and, where appropriate, this possibility should be discussed with the patient.

Withdrawal of AED treatment may be an option for patients on AEDs who have been seizure free for at least two years and such patients should be given the opportunity to discuss possible AED withdrawal with an epilepsy specialist *(see section 4.7)*.

D **A structured management system for patients with epilepsy should be established in primary care. As with other chronic diseases, an annual review is desirable.**

D **The annual review should be facilitated by specialist epilepsy nurses, linking primary care to the hospital system** (shared care)**.**

D **The shared care management system adopted should seek to:**

- **identify all patients with epilepsy, register/record basic demographic data, validate the classification of seizures and syndromes**
- **make the provisional diagnosis in new patients, provide appropriate information and refer the patient to a specialist centre**
- **monitor seizures, aiming to improve control by adjustment of medication or re-referral to hospital services**
- **minimise the adverse effects of medications and their interactions**
- **facilitate structured withdrawal from medication where appropriate, and if agreed by the patient**
- **introduce non-clinical interventions, and disseminate information to help improve the quality of life for patients with epilepsy**
- **address specific women's issues, and**
- **address the needs of patients with learning disabilities.**

D **Healthcare professionals who carry out structured primary-care reviews for patients with epilepsy should have attended an epilepsy training course in the past five years or be able to demonstrate equivalent experience from continuing professional development.**

D **Patients presenting to primary care with suspected first seizure or new epilepsy should be referred to an epilepsy specialist and asked to take an eyewitness or eyewitness contact details if available, to the appointment.**

D **Patients with treatment-resistant epilepsy should have the opportunity to receive shared care to enable accurate classification and tailored management of their seizures.**

D **Women of childbearing potential who are taking antiepileptic drugs should receive information about contraception, conception and pregnancy at their regular structured review in primary care and should have the opportunity to be referred to secondary care to have their diagnosis and treatment reviewed by specialist services before conception.**

D **Patients referred following a suspected first seizure or new epilepsy should be advised not to drive until they have seen an epilepsy specialist.**

D **Patients with epilepsy who hold a driving licence and who continue to have seizures should be made aware of current DVLA regulations.**

✓ All patients with epilepsy should receive an annual review within primary care which should be conducted face-to-face and should include questions on:

- seizure control, seizure frequency and date of last seizure
- antiepileptic drug dose, adherence and adverse effects
- mood and anxiety
- diet and lifestyle advice to reduce osteoporosis risk
- alcohol consumption.

✓ Healthcare professionals, at all levels, should be aware of the valuable contribution which can be made by the voluntary sector and should be proactive in highlighting the benefits of, and willing to signpost patients to, voluntary services for support and information.

9.2 MODELS OF SECONDARY AND TERTIARY CARE FOR EPILEPSY

No clear evidence was found to support any particular model of secondary or tertiary care for patients with epilepsy. A systematic review comparing specialist epilepsy clinics with general neurology clinics found insufficient evidence to demonstrate the superiority of any particular care model.[444] The authors concluded, however, that the failure to find an effect may be due to the poor quality of the information available and lack of adequate research, rather than a lack of effect of specialist clinics on outcomes. A retrospective cohort study of 200 patients in the USA found that subspeciality care improved seizure control in patients with drug-resistant epilepsy but concluded that further research is required to determine whether patients with drug-resistant epilepsy would benefit from routine referral to an epilepsy specialist.[445] **2+**

On the basis of evidence provided elsewhere in this guideline, the guideline development group have proposed the following core components of different types of service.

Table 7: Core components for epilepsy services in secondary and tertiary care

Service type	Requirements
District general hospital without neurology outpatient services	Access to medical and nursing epilepsy specialists for acute and complex cases Access to EEG for emergency management of *status epilepticus*
Teaching hospital or hospital with a neurology unit and outpatient neurology services	Specialist epilepsy clinics Epilepsy medical and nursing specialists Access to specialised neurophysiology investigations, such as EEG, for classification of epilepsy and management of *status epilepticus* Access to appropriate neuroimaging, such as MRI (preferably reported by specialist neuroradiologists) Access to specialised neuropsychology and neuropsychiatry services Access to inpatient facilities Access to a medium-term residential/monitoring facility (to allow formal medical, psychological, psychiatric, and neurophysiological assessment for those where there is diagnostic doubt or more complex needs) Specialist assessment and management of recent onset epilepsy Specialist management of patients with drug-resistant epilepsy
Tertiary referral centre	All services provided by teaching hospital or epilepsy clinic (see above), plus: Long-term EEG monitoring (with and without video and may include polysomnography) Access to epilepsy surgery Access to intracranial EEG monitoring for epilepsy surgery work up Access to specialist neuroradiology, with reporting by specialst neuroradiologists, including: • positron emission tomography and interictal single photon emission computerised tomography (SPECT) • functional imaging such as ictal SPECT and functional MRI

Current preferred practice is for epilepsy clinics to be developed in hospitals, however, where feasible, consideration can be given to developing epilepsy clinics in the community, for example within large primary-care group practices. Consideration should also be given to optimising care for specific groups such as:

- fast-track clinics for rapid diagnosis of new onset seizures and new epilepsy
- transition clinics for teenagers and young adults with epilepsy
- pregnant women with epilepsy
- individuals with learning disability who have epilepsy.

9.3 ROLE OF THE EPILEPSY SPECIALIST NURSE

A consensus document developed by a steering group of adult epilepsy specialist nurses (ESN) for the Royal College of Nursing,[446] describes the role of the adult ESN as including:

- the empowerment of people with epilepsy by providing information, support, and advice both to people with epilepsy and to carers and families
- the promotion of a greater understanding of the condition
- the adoption of a holistic, collaborative and co-ordinated approach that can help reduce the impact of epilepsy on the individual and their family.

4

The role of the ESN varies between secondary- and tertiary-service providers. Some ESNs are independent prescribers and adjustment of medication is a large part of their duties, some are part of multidisciplinary teams involved in the assessment of people with epilepsy being considered for epilepsy surgery, and some are involved in recruitment, supervision, training and appraisal of junior ESNs. When recruiting ESNs, NHS boards are advised to be aware of the wide scope and variation in ESN expertise, which depends upon the ESNs prior experience and educational attainment.[446]

One study showed that 70% of patients with epilepsy attending clinics run by ESNs had previously unidentified problems successfully resolved by the nurse including misdiagnosis, overmedication and lack of awareness of drug adverse effects.[447] 2^{+}

A systematic review found no evidence that ESN involvement reduced seizure frequency, seizure severity or quality of life, however, there was some evidence that ESN involvement might lead to improved knowledge of epilepsy in people with newly diagnosed epilepsy whose knowledge of epilepsy was poor. The poor quality of many of the included studies and heterogeneity of outcomes, study populations, interventions and timescales across the studies, however, limit interpretation of the results.[448] 2^{++}

The contribution of the ESN to patient care is recognised by the Clinical Standards for Neurological Health Services in Scotland which recommend that patients with a new diagnosis of epilepsy should receive an appointment with an ESN that takes place within 30 working days of the diagnosis.[442] 4

D **Each epilepsy team should include epilepsy specialist nurses.**

9.4 SELF MANAGEMENT

Evidence to support the promotion of self management in people with epilepsy is very limited. A systematic review of self-management strategies for adults with epilepsy identified only two poor-quality trials evaluating the effect of self management (with the intervention, in both, delivered during a two-day programme), both reporting high dropout rates of participants (35% and 62%). Seizure frequency decreased significantly in the intervention group in one trial but the other trial reported no significant difference in seizure frequency between the control and intervention groups. Other benefits reported in one trial included improved epilepsy knowledge, improved coping with epilepsy and improved tolerability of AED treatment. The other trial reported a significant increase in overall understanding of epilepsy, a significant decrease in fear of seizures, and a significant decrease in hazardous medical self-management practices. The extent to which these interventions are generalisable to other patients in other situations is not known nor is the benefit in the long term (assessment in the two trials included in the review was at four months and six months after the intervention).[448] 2++

Provision of information to people with epilepsy and their carers is covered in section 10.

✓ Patients with epilepsy should be provided with appropriately tailored information to expand their knowledge and understanding of their condition and its management.

10 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing epilepsy with patients and carers and in guiding the production of locally-produced information materials.

10.1 ADVICE AND INFORMATION ON EPILEPSY

People with epilepsy and their carers have a need for clear, accurate and appropriate information and advice. Surveys have reported that up to 90% of patients want more information and felt that they had received little advice about the cause of epilepsy, effects and interactions of drugs and the avoidance of potentially dangerous situations.[449, 450] Conversely, it is known that patients can forget or fail to take in much of what they are told during clinic visits so written information, and helpline telephone numbers and contact details of voluntary organisations should be given to all patients. People should be empowered to manage their condition as well as possible and information should be tailored to the person's needs.

Almost as important as the quality of information is the manner in which it is given. Many patients prefer talking to an epilepsy nurse or someone from a voluntary organisation with whom they feel more at ease.[451] Some information may have to be repeated on different occasions to ensure understanding. Patients with epilepsy place great importance on having a doctor who is approachable, communicative and knowledgeable and on receiving adequate information on their condition.[452]

A general information leaflet should be offered to all patients at the time of diagnosis. Epilepsy checklists are available from support organisations. Information for patients should be suited to their understanding, making adjustments for different developmental ages, gender, culture and stage of life of the person.[453] It should be noted that children are frequently carers of a parent with epilepsy, and need to be given proper support via voluntary organisations and carer's centres.

Guidelines for teachers have been produced by Epilepsy Scotland and there is a demand for their training in schools, colleges and universities. Information relating to outcomes from such training is currently lacking. A survey found that there had been little improvement in information provision despite the problem having been highlighted previously.[438] It was concluded that reducing the information deficit would significantly reduce the morbidity associated with epilepsy.

In Scotland, 4% of the population is from an ethnic minority background. Language, cultural issues, stigma and belief systems of people from black and minority ethnic groups may have an impact on an individual's access to information about their condition, their treatment and care, adherence to medication, and ability to cope with and manage their condition. Research is needed to identify any real or perceived barriers relating to diagnosis, receipt of information about epilepsy, and treatment for epilepsy, to allow healthcare professionals to take these into consideration when working with patients from BME groups.

- ✓ Information should be given in an appropriate manner with sufficient time to answer questions.
- ✓ Information should be repeated over time and reinforced to ensure understanding.
- ✓ Patients should be given information to take home in the most suitable format, for example leaflets, factsheets, a DVD, or specialised material for people with learning disability, making adjustments for patients from black and minority ethnic groups. All information and literature provided should be subject to regular review.
- ✓ Where appropriate, information about bilingual, and culturally-sensitive epilepsy materials and support services should be given.

✓ Healthcare professionals should be aware that the cultural differences and belief systems of patients from black and minority ethnic groups may have an impact on levels of understanding, management of the condition and adherence to medication and treatment.

10.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

General epilepsy information	**Possible psychological consequences**
Explain the following to patients and carers: • what epilepsy is* • probable cause, if known • explanation of investigative procedures • classification of seizures* • syndrome, if known • prognosis* • genetics, if appropriate • sudden unexpected death in epilepsy (SUDEP)* • bone health	Allow sufficient time to discuss the following issues: • perceived stigma and how patients view their epilepsy* • memory issues* • mood/anxiety disorders • maintaining mental well being* • self esteem*
Antiepileptic drugs	**Issues for women**
Discuss treatment options with patients and offer written and verbal information on: • choice of drug* • efficacy* • adverse effects* • adherence, including how it should be taken and dosage* • drug interactions* • action to take in case of missed or delayed medication • importance of consistency of supply • pharmacist resource	The following issues should be discussed with women and sufficient time given for them to ask questions: • contraception* • planning pregnancy* • pregnancy and breastfeeding*
Seizure triggers	**Lifestyle**
Ensure patients are aware that the following may trigger seizures: • lack of sleep* • alcohol and recreational drugs* • stress* • photosensitivity	Mention and discuss (if applicable) the following with patients: • driving regulations* • entitlement to a free bus pass • employment • education (eg Epilepsy Action Scotland guidelines for teachers and also Young Epilepsy) • leisure • relationships • safety in the home* • welfare benefits

First Aid	Format
Ensure patients' carers/relatives are aware of the following: • general first aid guidelines* • when to call an ambulance	The information offered should be appropriate to the patient's level of understanding, eg websites, audio, pictorial aids, and language specific The following should be considered: • literacy level of patient • learning disability • partially sighted • hearing difficulties • those whose first language is not English (consider interpreter services)
Sources of support	
• Ensure patients and carers (including children) are aware of where they can go to for further information and support *(see section 10.3)* • Regular review by GP • Information should be given in written format to aid patient understanding	

* These are considered to be the most important items and should be given at an appropriate time for the individual.

10.3 SOURCES OF FURTHER INFORMATION

Citizens Advice Scotland
Website: www.cas.org.uk

The Citizens Advice Bureau (CAB) can give free, confidential, impartial and independent advice and information on a wide range of subjects: benefits, debt and money advice, consumer issues, work-related problems and housing.

Epilepsy Action
New Anstey House, Gate Way Drive,Yeadon, Leeds LS19 7XY
Helpline: 0808 800 5050 • Free Fax: 0808 800 5555
Email: helpline@epilepsy.org.uk • Website: www.epilepsy.org.uk

The aim of Epilepsy Action is to raise awareness in their target audience about epilepsy, and to bring about permanent change for the social and medical benefit of people with epilepsy.

Epilepsy Connections
100 Wellington Street, Glasgow G2 6DH
Tel: 0141 248 4125 • Fax: 0141 248 5887
Email: epilepsyconnections.org.uk • Website: www.epilepsyconnections.org.uk

Forth Valley Fieldwork Service Administration Offices
Falkirk Community Hospital, Westburn Avenue, Falkirk, FK1 5SU
Tel: 01324 673750
Website: www.epilepsyconnections.org.uk

Epilepsy Connections provides information, advice and support to people with epilepsy and their carers on a one-to-one basis and to families and groups in the Greater Glasgow and Clyde and Forth Valley NHS board areas. Services include self-management support; advice about managing epilepsy at home, school, university or work; advice about housing, benefits, travel and balancing risk and safety; formal and informal counselling; befriending for adults; social activities for adults and children; epilepsy and memory workshops, epilepsy awareness and rescue medication training for paid and unpaid carers; epilepsy awareness sessions for students and teachers in schools and colleges. Information and advice is available in English, Urdu, Punjabi, Cantonese and Polish.

Epilepsy Consortium Scotland
enquiries@epilepsyconsortiumscotland.co.uk • www.epilepsyconsortiumscotlandscotland.co.uk

The Consortium is a collaboration of organisations and individuals in Scotland coming together to highlight epilepsy issues. This partnership has been developed to inform Scottish Government and other policy makers about areas of concern around health, social care and related public policy matters.

Epilepsy Scotland
48 Govan Road, Glasgow G51 1JL
Helpline: 0808 800 2200 • Fax: 0141 419 1709
Email: enquiries@epilepsyscotland.org.uk • Website: www.epilepsyscotland.org.uk

Orchard Brae House, 30 Queensferry Road, Edinburgh, EH4 2HG
Tel: 0131 226 5458

Epilepsy Scotland is the national organisation representing people living with epilepsy in Scotland. Services include Lighthouse Outreach, Community Support and Activity Groups; youth groups and social work support; campaigning and lobbying; policy; the provision of information and training. There is also a very experienced contact team who provide guidance, support and information on the telephone, via social media, email or text and in over 170 languages via a telephone interpretation service.

Epilepsy Society
Chesham Lane, Chalfont St Peter, Bucks SL9 0RJ
Helpline: 01494 601400 • Tel: 01494 601300 • Fax: 01494 871927
Website: www.epilepsysociety.org.uk

The Epilepsy Society provides epilepsy services throughout the UK. Through research, awareness campaigns, information resources and expert care, they work for everyone affected by epilepsy in the UK.

NHS 24
Freephone 111
Website: www.nhs24.com

NHS 24 is an online and out-of-hours phone service providing the Scottish people with access to health advice and information 24 hours a day, 365 days a year.

Quarriers Epilepsy Services (Scottish Epilepsy Centre and Epilepsy Fieldwork Services)
The William Quarrier Scottish Epilepsy Centre, 20 St Kenneth Drive, Glasgow, G51 4QD
Tel: 0141 445 7750
Email: Scottishepilepsycentre@quarriers.org.uk • Website: www.scottishepilepsycentre.org.uk

Quarriers
Quarriers Village, Bridge of Weir, PA11 3SX
Tel: 01505 612224/616000 • Fax: 01505 613906
Email: enquiries@quarriers.org.uk • Website: www.quarriers.org.uk

Quarriers is a Scottish charity providing practical support and care for children, adults and families at any stage in their lives.

Specialist Hospital Provision

The Scottish Epilepsy Centre is an independent hospital operated by the charity Quarriers. A national resource which provides specialist epilepsy assessment to patients throughout Scotland in parternship with the NHS, the Scottish Epilepsy Centre delivers flexible, person-centred, outpatient and inpatient care in a purpose -built national centre. This is provided by a specialist multidisciplinary team for people who pose diagnostic challenges, for individuals who have complex epilepsy and associated conditions. Referrals can be accepted from consultants associated with epilepsy care.

Epilepsy Fieldwork Service

Quarriers Epilepsy Fieldworker Services operate in Grampian and Fife. They work in the community with people with epilepsy, their families and carers, and other professionals who support them. They provide information and support after a new diagnosis and to those living with epilepsy. They advise about healthy lifestyle and encourage clients to manage their condition.

SUDEP Action
PO Box 112, Wantage, Oxon OX12 8XT
Bereavement Support Contact Line - 24 hour answering service: 01235 772852
Tel: 01235 772850
Email: epilepsybereaved@dial.pipex.com • Website: www.sudep.org

SUDEP Action is the leading organisation for relatives of people who have died from epilepsy. They offer information on risks of epilepsy, offer support when someone has died, sponsor research and education to prevent further deaths and capture data across the UK through the Epilepsy Deaths Register

UK Epilepsy and Pregnancy Register
Tel: 0800 3891248
Website: www.epilepsyandpregnancy.co.uk

The Register obtains and publishes information on the frequency of major malformations, such as heart defect, spina bifida and cleft lip, among infants whose mothers take one or more antiepileptic drugs (AEDs) to prevent seizures. Women with epilepsy who become pregnant, whether or not they are on treatment for epilepsy, are eligible to register.

10.3.1 CARING AND CARER ORGANISATIONS

Different non-governmental and voluntary sector organizations support Scotland's carers in their caring role and provide information, data and research on Scotland's carers. Some of these NGO/voluntary bodies are listed below, although please note this is not an exhaustive list:

Alzheimers Scotland
www.alzscot.org • Freephone: 0808 808 3000

Barnardo's Scotland
www.barnardos.org.uk/scotland.htm • Tel: 0131 446 7000

Carers Scotland
www.carerscotland.org/Home • Advice line: 0808 808 7777

Carers Trust Scotland
www.carers.org • Tel: 0300 123 2008

Children 1st
www.children1st.org.uk • Tel: 0131 446 2300

Coalition of Carers in Scotland
www.carersnet.org • Tel: 01786 825 529

Crossroads Caring in Scotland
www.crossroads-scotland.co.uk • Tel: 0141 226 3793

Minority Ethnic Carers of Older People Project (MECOPP)
www.mecopp.org.uk • Tel: 0131 467 2994

Scottish Young Carers Service Alliance
www.youngcarers.net • Tel: 0141 221 5066

Shared Care Scotland
www.sharedcarescotland.com • Tel: 01383 622 462

VOCAL
www.vocal.org.uk • Tel: 0131 622 6666

11 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

11.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN.

11.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

11.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

11.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

- In December 2012, SMC advised that perampanel (Fycompa®) is accepted for restricted use within NHSScotland (Ref SMC No. 819/12). The summary statement from SMC is included below.

  "Following a full submission perampanel (Fycompa®) is accepted for restricted use within NHSScotland.

  Indication under review: adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

  SMC restriction: use as a second-line adjunctive treatment in patients with refractory partial-onset epilepsy. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

  In three placebo-controlled studies in patients with uncontrolled partial-onset seizures, perampanel was superior to placebo in terms of the proportion of patients experiencing a ≥50% reduction in partial seizure frequency per 28 days.

  This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of perampanel. This SMC advice is contingent upon the continuing availability of the patient access scheme or a list price that is equivalent or lower."

- In October 2012 SMC advised that zonisamide (Zonegran®) is not recommended for use within NHSScotland (Ref SMC No.817/12). The summary statement from SMC is included below.

  "In the absence of a submission from the holder of the marketing authorisation zonisamide (Zonegran®) is not recommended for use within NHSScotland.

  Indication under review: monotherapy for the treatment of partial seizures (with or without secondary generalization) in adults with newly diagnosed epilepsy.

  The holder of the marketing authorisation has not made a submission to SMC regarading theis product in this indication. As a result we cannot recommend its use within NHSScotland."

- In July 2011, the SMC advised that retigabine (Trobalt®) is accepted for restricted use within NHSScotland (Ref SMC No. 712/11). The summary statement from SMC is included below:

  "Following a full submission retigabine (Trobalt®) is accepted for restricted use within NHSScotland.

  Indication under review**:** adjunctive treatment of partial-onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

  SMC restriction: patients with refractory epilepsy. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

  In two placebo-controlled studies in patients with refractory epilepsy retigabine was superior to placebo in terms of the proportion of patients experiencing 50% reduction in partial seizure frequency per 28 days. An indirect comparison indicates that retigabine has similar efficacy to two other antiepileptic drugs used as adjunctive therapy."

- In November 2010 SMC advised that eslicarbazepine acetate (Zebinix) is accepted for restricted use within NHSScotland (Ref SMC No. 592/09). The summary statement from SMC is included below.

  "Following a resubmission eslicarbazepine acetate (Zebinix) is accepted for restricted use within NHS Scotland.

  Indication under review: as adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.

  SMC restriction: patients with highly refractory epilepsy who have been heavily pretreated and remain uncontrolled with existing antiepileptic drugs.

  Eslicarbazepine acetate reduces seizure frequency compared to placebo over a 12-week maintenance period. Direct comparative data versus other antiepileptic drugs are unavailable, particularly comparisons with other cheaper agents with a very similar mode of action.

  This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of eslicarbazepine acetate. This SMC advice is contingent upon the continuing availability of the PAS in Scotland."

- In January 2009, the SMC advised that lacosamide (Vimpat®) is accepted for restricted use within NHSScotland (Ref SMC No. 532/09). The summary statement from SMC is included below.

  "Following a full submission lacosamide (Vimpat®) is accepted for restricted use within NHSScotland as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

  The proportion of responders was significantly greater with adjunctive lacosamide treatment compared to placebo. Lacosamide use is restricted to patients with refractory epilepsy and treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy."

- In February 2008, SMC advised that levetiracetam (Keppra®) is accepted for restricted use within NHSScotland (Ref SMC No. 397/07). The summary statement from SMC is included below.

  "Following a resubmission levetiracetam (Keppra®) is accepted for restricted use within NHSScotland as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

  Levetiracetam has been shown to be non-inferior to an older first-choice antiepileptic drug for partial seizures.

  Levetiracetam is significantly more expensive than traditional drugs so its use is restricted to patients for whom the range of traditional drugs normally used for first-line treatment are ineffective or unsuitable."

- In February 2008, the Scottish Medicines Consortium (SMC) advised that levetiracetam (Keppra®) is accepted for restricted use within NHSScotland (Ref SMC No. 396/07). The summary statement from SMC is included below.

  "Following a resubmission levetiracetam (Keppra®) is accepted for use within NHSScotland as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with generalised idiopathic epilepsy.

  In the pivotal study, addition of levetiracetam to existing anticonvulsant therapy achieved a significantly greater reduction in the frequency of primary generalised tonic-clonic seizures than addition of placebo."

- In December 2005, SMC advised that zonisamide (Zonegran®) is accepted for restricted use within NHSScotland (Ref SMC No. 216/05)

  "Following a full submission zonisamide (Zonegran®) is accepted for restricted use within NHSScotland as adjunctive therapy in adult patients with partial seizures, with or without secondary generalisation. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anticonvulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interaction or poor tolerance.

- In January 2005, SMC advised that pregabalin (Lyrica®) is accepted for restricted use within NHSScotland (Ref SMC No. 145/04). The summary statement from SMC is included below.

  "Following a full submission pregabalin (Lyrica®) is accepted for restricted use within NHSScotland as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

  It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anticonvulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interaction or poor tolerance."

- In January 2004 SMC advised that topiramate is accepted for restricted use within NHSScotland (Ref SMC No. 75/03). The summary statement from SMC is included below.

  "Following a full submission topiramate is accepted for restricted use within NHSScotland for its extended (monotherapy) indication. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

  Topiramate should be used principally in patients who have not benefited from treatment with an older anticonvulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interactions or poor tolerance. Its use for second-line therapy in epilepsy is unaffected by this recommendation."

12 The evidence base

12.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2001–2013. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

12.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to the diagnosis and management of epilepsy in adults. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

12.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex 1)*. The following areas for further research have been identified:

- What is the best first-line therapy for patients with focal seizures (comparison of new with old AEDs)?
- What is the best first-line treatment for patients with generalised seizures?
- What are the most effective combinations of antiepileptic drugs?
- What non-drug therapies (VNS *v* DBS) and surgical interventions are most effective for different types of seizure?
- Is there significant benefit in regular therapeutic drug monitoring with newer AEDs compared to older AEDs?
- In which patients is it acceptable to freely switch brands of AED?
- What second-line drugs for generalised *status epilepticus* are most effective (comparison of all commonly used drugs)?
- In patients with newly diagnosed epilepsy, does routine EEG significantly improve outcomes?
- How should bone disease be screened for in those with epilepsy on AEDs?
- How should fractures be prevented in people with epilepsy on AEDs who have a high risk of osteoporosis?
- What is the most effective AED to treat seizures in those with Down's syndrome and dementia?
- Do pregnancy and perinatal outcomes following induction of labour and Caesarean section in women with epilepsy differ from those where induction of labour or Caesarean section are not performed?
- Do postpartum haemorrhage rates in women with epilepsy taking AEDs and those not taking AEDs differ from those in women without epilepsy?
- Are perinatal outcomes adversely affected in women with epilepsy taking antiepileptic drugs during pregnancy and how do outcomes differ for different AEDs?
- Does menopause increase or reduce seizure frequency in women with epilepsy and are effects linked to AED treatment?
- What effect does HRT have on seizure frequency in postmenopausal women with epilepsy and are effects related to AED treatement?

- What mechanisms, other than folic acid depletion, explain the teratogenic effect of antiepileptic drugs?
- Does assistive technology have a place in helping to address memory problems in people with temporal lobe epilepsy?
- How effective are cognitive rehabilitation strategies that target executive function impairment in improving mood, planning and reasoning in those with planning and attention deficits who suffer from epilepsy?
- How effective is education in supporting families to help maintain use of compensatory memory strategies by relatives who suffer from epilepsy?
- What are the optimum models of care for epilepsy in community-, secondary- and tertiary-care?

12.3 REVIEW AND UPDATING

This guideline was published in 2015 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

13 Development of the guideline

13.1 INTRODUCTION

SIGN is a collaborative network of healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

13.2 THE GUIDELINE DEVELOPMENT GROUP

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

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Karen Graham	*Patient Involvement Officer*
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Stuart Neville	*Publications Designer, SIGN Executive*
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SIGN would like to acknowledge the contribution made by the following people during the early stages of guideline development.

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13.2.2 EXPERT PANEL FOR SEPTEMBER 2018 UPDATE

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13.3 CONSULTATION AND PEER REVIEW

13.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 3 February 2014 and was attended by 105 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

13.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

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SIGN is also grateful to the following organisations for their contribution to the guideline.

Association of British Neurologists

Royal College of Physicians, Edinburgh

13.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website **www.sign.ac.uk**

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Abbreviations

ADR	adverse drug reaction
AED	antiepileptic drug
BDI	Beck's Depression Inventory
BME	black and minority ethnic groups
CBT	cognitive behaviour therapy
CES-D	Centre for Epidemiological Studies Depression Scale
COCP	combined oral contraceptive pill
CM	congenital malformation
CPAP	continuous positive airway pressure
CT	computed tomography
DBS	deep brain stimulation
ECG	electorcardiography
EEG	electroencephalography
ESN	epilepsy specialist nurse
GGE	genetic generalised epilepsies
GTCS	generalised tonic-clonic seizure
HADS-D	Hospital Anxiety Depression Scale Depression sub scale
HLA	human leucocyte antigen
HR	hazard ratio
HrQoL	health-related quality of life
HRT	hormone replacement therapy
ICD-10	International Classification of Diseases, 10th revision
ILAE	International League Against Epilepsy
IM	intramuscular
IQ	intelligence quotient
ITU	intensive treatment unit
IV	intravenous
MA	marketing authorisation
MCM	major congenital malformation
MRI	magnetic resonance imaging
MTA	multiple technology appraisal
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
NICE	National Institute for Health and Care Excellence
NTD	neural tube defect
OR	odds ratio

OSA	obstructive sleep apnoea
PGES	prolonged postictal generalised EEG suppression
PHQ-2	patient health questionnaire 2
PSG	polysomnography
QoL	quality of life
RCT	randomised controlled trial
SGA	small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMR	standardised mortality ratio
SPECT	single photon emission computerised tomography
SUDEP	sudden unexpected death in epilepsy
VNS	vagus nerve stimulation
WHO	World Health Organisation

Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	See guideline section
1. What is the sensitivity and specificity of short-term video-EEG, videotelemetry (VT), polysomnography and hand-held video capturing (ie phones) in diagnosing epilepsy?	3.4, 3.5
2. What is the sensitivity and specificity of 24-hour hour cardiography, routine ECG, implanted loop recorders in diagnosing cardiac arrhythmias causing collapses that are mistaken for epilepsy?	3.7
3. In adults with newly diagnosed epilepsy are levetiracetam and zonisamide monotherapies more effective and well tolerated than existing AEDs at reducing seizure frequency, seizure duration, and adverse effects, and improving recovery time and QoL?	4.2
4. In adults with epilepsy what is the evidence that switching between drug brands (brand and generic) results in worsening seizure control and adverse effects?	4.2
5. Once monotherapy has failed what adjunctive drugs (eslicarbazepine, lacosamide, pregabalin, retigabine, rufinamide, perampanel) are most effective and well tolerated compared to existing add-on therapies or to placebo?	4.3
6. In adults with epilepsy is there evidence that there are any combinations of drugs (rational polytherapy) that are more effective and well tolerated than other combinations?	4.3, 4.6
7. In adults with epilepsy being treated long term with AEDs is there evidence that it adversely affects BMD compared with those not taking AEDs?	4.6.4
8. In adults with drug resistant epilepsy is VNS or DBS more effective than current treatment or placebo for reducing seizure frequency, seizure duration and adverse effects and improving recovery and QoL?	4.9.1, 4.9.2
9. In adult patients with *status epilepticus* what is the best drug regime for stopping seizures?	4.10
10. In adults with a history of prolonged and serial seizures, which drug regime is most effective at reducing seizure duration, severity and improving recovery time? *Consider*: midazolam maleate, midazolam hydrochloride, rectal diazepam, buccal lorazepam, what form of benzodiazepine?	4.11
11. In people aged 65 or over with epilepsy which AEDs have superior efficacy and tolerability? *Consider*: carbamazepine, phenytoin, phenobarbital, primidone, sodium valproate, ethosuximide, clobazam, vigabatrin, gabapentin, lamotrigine, levetiracetam, topiramate, tiagabine, pregabalin, zonisamide, oxcarbazepine, rufinamide, eslicarbazepine, lacosamide, retigabine, perampanel	4.14
12. In people aged 65 or over with epilepsy (with or without dementia) how does QoL differ compared to older people without epilepsy? *Consider*: multidisciplinary shared care	4.14.1, 4.14.4
13. In people with epilepsy is there any evidence for the management of epilepsy in people with Down's syndrome and dementia?	4.15
14. In women with epilepsy taking hepatic enzyme-inducing AEDs or non-inducing AEDs, what advice should be given regarding contraception, including postnatal contraception, and emergency contraception? *Consider*: combined oral contraceptive pill, progesterone only pill, progesterone implant, levonorgestrel intrauterine system, transdermal patches, condoms, IUCD, levonorgestrel emergency contraceptive pill	5.1

15. In women with epilepsy what evidence is there that pre-pregnancy counselling (including genetic and breastfeeding counselling) improve seizure control and pregnancy outcomes and reduce teratogenicity, compared to women who do not receive counselling? *Consider*: women taking and not taking AEDs	5.2
16. For women with epilepsy taking AEDs and prescribed folic acid (folate) for the prevention of neural tube defects, what evidence is there to guide healthcare professionals on: • daily dose of folic acid (folate) – 5 mg versus 400 micrograms • duration of prepregnancy folic acid (folate) dosing (1 month versus 3 months versus longer) • duration of folic acid (folate) dosing during pregnancy (first 12 weeks (first trimester) versus entire pregnancy?	5.2.1
17. What factors relating to a woman's epilepsy (particularly seizure type) will affect the outcome of her pregnancy?	5.2–5.5
18. In pregnant women with epilepsy taking AEDs how should management differ during the antenatal period, labour, delivery and the postnatal period, compared to pregnant women without epilepsy? *Consider*: multidisciplinary shared care	5.4–5.5
19. In pregnant women with epilepsy who receive AEDs as monotherapy or in combination what evidence is there that there is an increased risk of adverse pregnancy outcomes, teratogenicity and epilepsy in offspring, compared to pregnant women with epilepsy not on AEDs, and pregnant women without epilepsy?	5.4–5.6
20. In pregnant women with epilepsy taking AEDs what evidence is there that those who undergo AED regimen manipulation and monitoring of AED circulating plasma concentrations have better maternal and perinatal outcomes than women with epilepsy taking AEDs who do not?	5.4.2
21. In pregnant women with epilepsy taking hepatic enzyme-inducing AEDs (at presumed risk of haemorrhagic disease of the newborn) how does the maternal administration of oral vitamin K from 36 weeks affect the incidence of haemorrhagic disease of the newborn, compared to those taking enzyme inducing AEDs who do not receive oral vitamin K, women with epilepsy taking non-inducing AEDs, and women without epilepsy?	5.4.3
22. In menopausal women with epilepsy taking AEDs what advice should be given on: • seizure control, • hormone replacement therapy?	5.9
23. In people with epilepsy what evidence is there that AEDs cause psychiatric and behavioural adverse effects and in what patient subgroups is this particularly prevalent (eg learning or intellectual disability or geriatric)? *Consider*: anxiety, irritability and aggression	6
24. In adults with epilepsy what validated diagnostic or screening tools or ratings scales are effective in determining the presence or absence of significant depression, psychosis or anxiety? *Consider*: HADS-D, BDI, NDDI-E, etc.	6.1
25. Does screening for depression and low mood lead to improved adherence, frequency and HrQoL?	6.1, 6.2
26. In adults with epilepsy which talking therapies are shown to be most effective in improving mood and seizure frequency? *Consider*: cognitive behavior therapy, acceptance and commitment, mindfulness, psychotherapeutic, positive psychology	6.2.1
27. In adults with epilepsy and depression which psychotropic (antidepressant) drugs are shown to be most effective in improving depression and non-exacerbation of seizures?	6.2.2

28. Does cognitive rehabilitation lead to improvement in medication adherence, HrQoL, mood and seizure frequency? *Consider*: neuropsychology, memory, learning, executive function	6.2.3
29. In adults with epilepsy does sleep apnoea exacerbate seizures and does treating it reduce seizure frequency?	7.2
30. In adults with epilepsy what is the evidence that risk factors, interventions and methods of communication affect the incidence and management of SUDEP? *Consider*: drug adherence, bed alarms, night-time supervision, seizure type and frequency, information given, pillows etc.	8
31. For adults with epilepsy what models of care (general practice, hospital-based specialist care, shared care, epilepsy specialist nurses, general medical, neurology clinics) improve patient outcomes in terms of seizure frequency, seizure severity, patient satisfaction and QoL?	9.1–9.3
32. Do adults with epilepsy, who are educated in self management, when compared with those who are not, have better health outcomes in terms of seizure frequency, seizure severity, patient satisfaction and quality of life?	9.4

Annex 2

Prepregnancy counselling list

Topic	Guideline section
Risks to the fetus from maternal smoking	5.2
Folic acid use	5.2.1
Adherence/concordance	5.2
Risk to the fetus and mother from seizures	5.6.1
Risk to the fetus exposed to AEDs	5.6
Inheritance	5.3
Model of care (epilepsy and obstetrics)	5.4
Effects pregnancy can have on epilepsy	5.4
Effects epilepsy can have on pregnancy	5.4
Antiepileptic drug levels	5.4.2
Obstetric outcomes	5.5
Planning and advice in the postpartum (consider multidisciplinary approach)	5.7
Breastfeeding	5.8

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