THE BARE ESSENTIALS

Epilepsy

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► An appendix containing a seizure recurrence formula is published online only at http://pn.bmj.com/content/vol8/issue3

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The diagnosis and management of epilepsy involves many disciplines, especially neurology, psychiatry, learning disability, general practice, paediatrics, geriatrics, emergency medicine and cardiology. A major challenge is to coordinate all the currently provided services.

EPIDEMIOLOGY

Epilepsy incidence is 5 per 10 000 per year. Among patients with suspected "first seizures", most have syncope, many others have provoked seizures, especially by alcohol.

Epilepsy prevalence is 7.5 per 1000. Among those prescribed antiepileptic drugs (AEDs) for recurrent episodes, 20% do not have epilepsy, most often psychogenic non-epileptic attacks.

DIFFERENCES FROM OTHER CHRONIC CONDITIONS

- **Public misconceptions**. Seizures seen by lay people, in life or on screen, are often the frequent seizures of the severely learning disabled (reinforcing a stereotype), or psychogenic (reinforcing ideas of seizures provoked by emotion), or provoked by flashing lights (not common), or with associated aggression (rare).
- **Low profile**. People with epilepsy often underachieve having missed education and career opportunities, making them poorly placed to advocate for better services. Those who could make a difference—for example, celebrities in the public eye—almost invariably conceal their condition.
- **Intermittent disorder**. Epilepsy is a background threat rather than an obvious disability with any stigma deriving more from concern about having seizures (felt stigma) than actually having them (enacted stigma).
- **All ages**. Epilepsy affects neonates to the elderly, and generally is long-term; its cumulative lifetime prevalence and morbidity is far greater than comparably prevalent adult-onset chronic neurological disorders such as stroke or multiple sclerosis.
- **Many conditions**. There are many causes and types of epilepsy and many more conditions that resemble epilepsy, so the diagnosis of "blackouts" requires a broad clinical perspective.
- **No test**. There is no one test for epilepsy, despite the public's and many clinicians' often misplaced faith in the EEG, and no test for seizure control (unlike diabetes and HbA1c).
- **No "trial of treatment"**. Epilepsy diagnosis is often difficult, but tablets are not an easy option; being prescribed AEDs imprints a diagnostic label and is seldom diagnostically helpful.
- **Overdiagnosis**. Epilepsy is often over-diagnosed and AEDs given unnecessarily. Blackout diagnosis relies on careful history taking and is, therefore, labour intensive; no costly machinery replaces quality time with an experienced clinician.

DIFFERENTIAL DIAGNOSIS

The core business of epilepsy clinicians is distinguishing seizure, syncope, and psychogenic attacks; other causes are far less common. Epilepsy is suggested by stereotyped, unprovoked events, either without warning or with a characteristically "indescribable" aura, events with automatisms, posturing, convulsions, lateral tongue biting and post-ictal confusion—for example, waking up in an ambulance.

Syncope

- **Vasovagal syncope** is suggested by the situation (bathroom, restaurant, aeroplane, etc), prodrome (hot, prickly, nauseated, visual darkening, pallor), brief unconsciousness (with or without uncoordinated jerks) and subsequent rapid orientation but prolonged fatigue. Cough and micturition syncope are variants. Several features may mimic seizures (myoclonic jerks, head turning, automatisms, incontinence).
- **Cardiac syncope** is suggested by cardiac symptoms, abnormal ECG, abrupt unprovoked collapse, brief unconsciousness, and rapid recovery.
- **Others** include orthostatic syncope (autonomic failure, elderly, anti-parkinsonian medications), and carotid sinus syncope (elderly).

Psychogenic episodes

- **Panic attacks** are suggested by the circumstances (for example, shops, crowds, in bed but not asleep), slow build up with increasing anxiety, breathlessness, tingling, blurred vision, long duration and tearfulness.
- **Dissociative convulsions** (pseudoseizures) may begin as panic, before a prolonged (many minutes) convulsion, with much movement (pushing, flailing), closed eyes and mouth,

resisting eye opening or eye contact, rapid breathing or breath holding in inspiration, and tearfulness. Features previously considered exclusively non-organic—for example, pelvic thrusting and bicycling—can occur in frontal lobe seizures.

Other causes

- **Parasomnias** resemble frontal lobe seizures, but usually with single rather than multiple events, and occurring earlier in the night rather than later.
- **Migraine** can cause loss of consciousness, but usually gradual onset with typical migraine symptoms.
- **Hypoglycaemia,** though rare, should always be considered, especially sleep-related episodes, before meals or after exercise, those associated with abnormal behaviour and AED-unresponsiveness, and in diabetics on blood glucose lowering drugs.

CLINICAL FEATURES

History taking

- **Adequate time** is crucial; there is no short cut.
- **Witness account** is ideal, despite clinician inconvenience—for example, telephoning from clinic.
- **Previous notes and investigations** (contemporaneous history, EEG before medication) are essential, even if troublesome to obtain.
- **Direct questions for other events** may identify myoclonus or minor seizures, or hint at sleep-related events (blood on pillow, bitten tongue).
- **Medications** - those that are epileptogenic (tramadol, neuroleptics) or syncope-inducing (vasodilators causing postural hypotension; drugs provoking long QT, see http://www.torsade.org).
- **Previous history** - early life events (gestation, birth history and weight, incubator, febrile seizures, cerebral infection or significant head injury) and psychiatric problems (depression, panic disorder, overdose, self-harm).
- **Family history** of fits, faints or blackouts, but also (in view of cardiac mimics) of sudden or young deaths.
- **Lifestyle issues** - driving, alcohol, relationships, education, occupation, leisure, pregnancy, contraception, etc.

Examination

Notwithstanding neurological tradition, the physical examination adds little in patients with blackouts; its greatest value is in offering opportunity for additional history away from parents/carers (if in a separate cubicle) and for reassuring patients of the clinician's thoroughness. However, productive areas are:

- **Skin** - tuberous sclerosis, café au lait patches, haemangioma, craniotomy scar, and wrists (previous self-harm).
- **Cardiovascular examination** can be more important than neurological examination—for example, irregular pulse.
- **Neurological examination** should include visual fields (for example, upper homonymous quadrantanopia in temporal lobe tumours), fundi, and search for lateralising signs. In new onset focal epilepsy it is worth identifying hemi-smallness (by comparing thumbnail sizes for subclinical hemiparetic cerebral palsy) and cranial bruit (for intracranial vascular malformation**).**
- **Seeing seizures** greatly facilitates their correct diagnosis. Patients or carers might make video (or mobile phone) recordings of the events.

CLASSIFICATION

Seizures and epilepsy are classified according to the 1989 Commission on Classification and Terminology of the International League Against Epilepsy (6).

Seizure classification

Seizures are categorised as generalised, focal or unclassified on clinical and EEG grounds. Complex partial (loss of awareness) and simple partial (retained awareness) are terms still used despite the overlap in ictal retention of consciousness.

Secondarily generalised tonic-clonic seizures

Most generalised convulsions starting in adulthood are secondarily generalised. Convulsions in sleep are usually secondarily generalised, whereas convulsions on awakening are typically primary generalised.

Temporal lobe seizures

- **Slow head turn** at onset suggests an ipsilateral focus (head turns towards seizure focus); subsequent forced head turning is contralateral (adversive, away from seizure focus).
- **Automatisms** (fidgeting, picking) characteristically are ipsilateral to the seizure focus; dystonic limb posturing is contralateral.
- **Nose wiping** towards seizure end is characteristically mesial temporal, but non-lateralising.
- **Ictal spitting, vomiting, coughing, and peri-ictal water drinking** all suggest non-dominant temporal involvement.
- **Unilateral eye blinking** is rare, but suggests an ipsilateral medial temporal focus.
- **The final limb jerk** in a secondary generalised seizure is characteristically ipsilateral.

Frontal lobe seizures

The frontal lobe's large size is reflected in the breadth of its seizure types:

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- **Jacksonian seizures** show a "march" of limb jerking, often spreading from the thumb, occasionally with post-ictal transient focal weakness (Todd's phenomenon).
- **Adversive seizures**—forced head and eye turning away from the seizure focus, with arm jerking or elevation ("fencing") contralateral to the focus.
- **Supplementary motor area seizures** are characteristically brief (<30 seconds), frequently from sleep, often with retained consciousness, and with "hypermotor" phenomena—for example, running, punching, shouting, cycling. The surface ictal EEG may even be unchanged, reflecting the deep midline seizure onset. The combination of bizarre behaviour and normal ictal EEG risk their mislabelling as psychogenic.
- **Speech arrest or dysphasia** suggests dominant hemisphere involvement; clear ictal speech is more likely non-dominant.

Occipital lobe seizures

Occipital seizures present with contralateral visual hallucinations—for example, lights or colours, but with ipsilateral eye deviation to the side of the focus. There is clinical overlap with migraine.

Parietal lobe seizures

Parietal seizures are rare and characterised by lateralised positive sensory disturbance—for example, tingling or pain contralateral to the focus.

Epilepsy classification and syndromes

Epilepsy classification is commonly overlooked but important for management and prognosis, and depends on two characteristics.

- **Site of seizure onset** determines an epilepsy as being either *generalised*, *focal* (a simpler term than localisation-related) or *unclassified*.
- **Presumed aetiology** is *symptomatic* (a known structural cause), *probable symptomatic* (or *cryptogenic*, where a structural cause is presumed but cannot be identified), or *idiopathic* (implying more than "unknown cause", but rather a presumed genetic cause with age-specific seizure onset and offset, normal brain imaging, and an expected good AED response).

Idiopathic generalised epilepsies

- **Juvenile myoclonic epilepsy**. Morning myoclonus, generalised tonic-clonic seizures on awakening, sometimes absences and photosensitivity—all more likely following sleep deprivation. Typically begins in adolescence but, despite its name, the epilepsy tendency tends to persist lifelong. The EEG usually contains inter-ictal generalised polyspike-and-wave.
- **Other syndromes** include juvenile absence epilepsy, generalised tonic-clonic seizures on awakening, and eyelid myoclonia with absences.

Symptomatic focal epilepsies

- **Hippocampal (mesial temporal) sclerosis** is the commonest cause of adult epilepsy. The typical history is of an early life cerebral insult—for example, prolonged focal febrile seizure, a latent interval of sometimes many years, then onset of complex partial seizures characteristically with epigastric aura.
- **Other symptomatic focal epilepsy** causes include head injury (typically frontal and temporal lobe involvement), tumours (especially low-grade tumours involving cortex, causing treatment-resistant, frequent simple partial seizures), cortical dysplasias (ranging from minor focal areas with normal intellect to generalised cortical abnormality with severe intellectual disability), arteriovenous malformations and cavernous malformations.

Idiopathic focal epilepsies

- **Benign epilepsies of childhood** are easily treated and often self-remitting—for example, benign childhood epilepsy with centrotemporal spikes, benign occipital epilepsy.
- **Monogenic focal epilepsies** are increasingly recognised—for example, autosomal dominant nocturnal frontal lobe epilepsy, and familial temporal lobe epilepsy with variable phenotype severity.

Symptomatic and cryptogenic generalised epilepsies

These include the severe childhood onset epilepsies typically associated with intellectual disability—for example, Lennox-Gastaut syndrome, myoclonic astatic epilepsy.

INVESTIGATIONS

All new onset unprovoked seizures must be investigated: the adage that everyone is allowed one seizure is nonsense and potentially dangerous.

Brain imaging

This is indicated for all new-onset unprovoked seizures in adults.

- **Computed tomography** is more available than MR, making it sometimes the appropriate initial investigation.
- **Magnetic resonance imaging** is the modality of choice, being more sensitive than CT to structural causes of epilepsy—for example, hippocampal sclerosis, cortical malformations, and benign cortical tumours (ganglioglioma and dysembryoplastic neuroepithelial tumour, etc). Hippocampal volume loss is more important than signal change; there may be associated volume loss in the ipsilateral temporal lobe and fornix. Not all MR scans are equal: adequate epilepsy imaging requires a standard detailed protocol, with reporting by a neuroradiologist. Current best practice is for MR imaging in all adult-onset epilepsy, apart from

those with clinically definite idiopathic generalised epilepsy.

- **Functional imaging** (functional MR, MR spectroscopy, magnetoencephalography) adds additional information, potentially identifying resectable focal abnormalities in MR-negative patients. MR tractography can map the visual pathway facilitating safer surgical resection.

Electroencephalography

- **Standard inter-ictal EEG** may indirectly indicate an epilepsy tendency; however, it is an adjunct to diagnosis, not to be relied upon alone. It is more useful in children and adolescents than adults. The first EEG before starting treatment is usually the most valuable and worth tracking down. Videotaping during all EEG recordings enhances their value should any events occur. EEG sensitivity is enhanced by longer recordings (time consuming and expensive), arranging it within 72 h of events (requiring rapid access), and following sleep deprivation (increased seizure risk).
- **Prolonged video EEG** capturing actual seizures is the gold standard, but even then some epilepsies with deep-seated foci have an unchanged surface EEG during attacks.

Electrocardiography

This is indicated for all undiagnosed blackouts, for all syncope presenting to neurologists, and resistant epilepsy, especially where imaging and/or EEG are normal. Neurologists should learn to assess ECGs systematically, measure the QTc interval, and recognise the ECG patterns of rare but potentially fatal and often familial, cardiac disorders, such as long QT syndromes and hypertrophic cardiomyopathy.

MANAGEMENT

Epilepsy management aims at seizure freedom without adverse drug effects which is realistic and achievable in most cases. People with epilepsy need long-term follow-up, maybe in primary care, but even those seizure free and coping with medication deserve regular specialist contact. In practice, few adults are suitable for permanent discharge from secondary care; some arrangements for contact with specialist services—for example, telephone, email—would be ideal.

Antiepileptic drugs (AEDs) (see table)

- **Diagnostic certainty**. It is almost always better to await a definite diagnosis rather than to start perhaps a lifetime of medication without diagnostic certainty.
- **Is any AED necessary**? AEDs are usually not recommended following a first seizure.
- **Long-term treatment**. The decision to prescribe AEDs is major and long-term, and taken jointly by patient and epilepsy specialist following informed discussion.
- **Choosing AEDs**. All available AEDs are potentially effective for focal epilepsies; although most AEDs can control generalised tonic-clonic seizures, some (for example, carbamazepine) may actually worsen myoclonus and absences: the choice for idiopathic generalised epilepsy is therefore more limited. The SANAD study suggested lamotrigine as the first choice for focal epilepsy and valproic acid the first choice for generalised epilepsy.
- **Sex differences** in AED adverse effects mean different choices for men and women—for example, oral contraceptives and pregnancy (see below).
- **Monotherapy** is preferred, starting with established medications (for example, carbamazepine, lamotrigine or valproate) then sequential monotherapy should the first choice fail. The first monotherapy gives seizure freedom in 47%, the second in a further 13% and the third in a further 4%; thus the first monotherapy response predicts the overall outcome.
- **Randomised controlled trials evidence** does not easily translate into clinical practice. Their main aim is licensing, so they are short-term, mostly using polytherapy in resistant epilepsy, often with doses higher than those used subsequently in clinical practice. The relevance to individuals of 50% seizure reduction as the principal outcome measure is also questionable.
- **Adverse effects**. Short-term problems are well documented from clinical trials: almost all AEDs potentially cause sedation. Longer-term adverse effects may emerge only after years; the nine years to recognise that over half taking vigabatrin developed permanent visual field defects justifies caution in judging the long-term safety of all new drugs.
- **Drug interactions**. Although interactions with other AEDs, warfarin or digoxin present difficulties, the most important interaction in adult practice is with the contraceptive pill, especially as failure exposes potential teratogenicity. Enzyme inducers (for example, carbamazepine, phenytoin and phenobarbital) clearly interact and require additional contraceptive precautions. Others interact only at higher doses—for example, topiramate, lamotrigine and possibly zonisamide. Nonetheless, caution is required as initial pharmaceutical company reassurance is sometimes later superseded.
- **Rational prescribing** uses known AED mechanisms to facilitate choice and minimise additive adverse effects. Rational polytherapy avoids combinations with similar mechanisms (for example, carbamazepine with lamotrigine); rational monotherapy uses sequential AEDs with differing mechanisms.
- **Once or twice daily** prescription is possible for all AEDs (except gabapentin) and clearly preferable; a midday dose taken to school or work is often forgotten and generates stigma.

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- **Brand names** are more acceptable when prescribing for epilepsy than elsewhere in medicine, especially for slow release formulations—for example, of carbamazepine. Minor changes in formulations may alter drug availability with potential breakthrough seizures, and patients are understandably nervous about changes to their drug brand and consequent threat to livelihood.
- **Blood levels** are generally unnecessary except when using phenytoin.
- **Free AED prescriptions** apply to many countries including the UK.
- **Medication concordance** with prescribed medication may be poor for several reasons: fear or experience of adverse effects, inadequate understanding of the indications, complacency after seizure freedom, rebellion against authority, decisions to conceive, etc.
- **Withdrawing AEDs** in children is relatively straightforward, usually when two years seizure free; several age-specific syndromes of childhood allow a reasonable chance of success. It is more difficult for adults with considerable pressure to remain seizure-free (retaining driving privileges, employment, freedom from stigma, social status, etc). Thus adults commonly remain on AEDs, even when many years seizure-free. The recurrence risk following AED withdrawal, derived from randomised controlled trials, can help patients in decision-making. See seizure recurrence formula online.

Tonic-clonic status epilepticus

Status epilepticus—seizures for >30 min without consciousness recovering in between—is an uncommon medical emergency. However, tonic-clonic seizures lasting >5 min (status in evolution) are common (5% of patients), justifying urgent intervention to prevent secondary neurological damage.

Management

Check blood glucose immediately (also biochemistry, toxicology, AED levels) but generally do not delay treatment for the results. At each stage, consider "status pseudoepilepticus" (almost 50% of apparent status admitted to adult intensive care).

- **Immediate**. ABC (airway, breathing, circulation), intravenous thiamine 100 mg (alcoholism suspected) or intravenous 50% glucose (hypoglycaemia identified).
- **Early** (1–10 min).
  - *Community*: buccal midazolam 0.2–0.4 mg/kg.
  - *Hospital*: intravenous lorazepam 0.1 mg/kg repeated if necessary at two min.
- **Established** (5–30 min). Intravenous phenytoin infusion (15–20 mg/kg over 20–30 min) with cardiac monitoring.
- **Refractory** (30–90 min) in intensive care unit. Intravenous phenobarbital (20 mg/kg, 100 mg/min) and/or intubate and ventilate under general anaesthetic (thiopentone, midazolam or propofol), aiming for EEG (continuous monitoring) of "burst suppression" or deeper, woken 2–4 hourly initially to check for seizure remission.

Lifestyle aspects

- **Partnership of care**. Effective epilepsy management requires the sharing with patients of verbal and written information about lifestyle and balance of risks, encouraging joint decision-making, and facilitating patient responsibility for epilepsy self-management. Useful patient information sources are available at Epilepsy Action (http://www.epilepsy.org) and National Society of Epilepsy (http://www.epilepsynse.org).
- **Challenge assumptions**. Both patients and clinicians may accept inadequate control or AED adverse effects, yet the range of available treatments suggests that often more can be done.
- **Lifestyle restrictions**. "You can do everything you did before, except drive" overstates the position, but emphasises that everything except driving is negotiable, given an appreciation and understanding of the balance of risks.
- **Driving**. Eligibility rules vary throughout the world, placing differing responsibilities on clinicians. The UK ordinary (Group 1) driving licence currently requires one-year freedom from all seizures, no matter how minor, or an established pattern of sleep-related seizures only for three years or more. Group 2 drivers (heavy goods and passenger vehicles) must be seizure-free and off all AEDs for 10 years before eligible to drive. Group 1 entitlement is based on a less than 20% annual seizure recurrence risk; Group 2 on a less than 2% annual risk.
- **Pregnancy**, now or later, dominates the AED prescribing decision in women. The UK epilepsy and pregnancy register (fig) provides useful guidance on major malformation rates with common AEDs but the data are observational rather than randomised, acquired only through pregnancy despite advice or by mistake; there is very limited information on the newer AEDs; valproate may have been selected for certain epilepsies, the genetic basis of idiopathic epilepsies giving possible greater fetal abnormality risk; taking valproate in pregnancy sometimes reflects poor access to or interest in optimal antenatal care; and pregnancy registers mostly do not address concerns about valproate or other AEDs causing neuro-developmental delay.
- **Regular sleep pattern** is an important part of self-management, especially in idiopathic generalised epilepsies.
- **Alcohol** in moderation is fine—for example, 2–4 units in 24 h. Some alcohol consumption is important for social participation in teenagers. Although alcohol is in theory anti-epileptic,

Table 1 The major antiepileptic drugs

Drug	Mechanisms and kinetics	Prescribing	Adverse effects	Interactions
Carbamazepine	▶ Stabilises voltage-gated sodium channels ▶ Strongly protein bound, highly lipid soluble, liver metabolised (active metabolite 10,11-epoxide)	▶ Partial-onset and generalised tonic clonic seizures (not absence or myoclonus) ▶ Start 100 mg daily, maintenance 400–1600 mg ▶ Frequency: 2× daily; 3× daily at >800 mg (half-life 5–26 h) ▶ Slow release preparations preferred to minimise adverse effects and allow twice-daily prescription ▶ In elderly on diuretics check electrolytes before prescribing. If seizures persist despite carbamazepine, check serum sodium	▶ Dose-related. Tiredness, dizziness, unsteadiness, diplopia ▶ Idiosyncratic. Rash (5%), neutropenia, inappropriate antidiuretic hormone secretion ▶ Teratogenicity. Spina bifida rate increased but reasonably safe (fig)	▶ Effect on others: lowers warfarin, steroids (including the contraceptive pill), lamotrigine, phenytoin, phenobarbital. Increases carbamazepine epoxide, giving toxic symptoms ▶ Effect of others: reduced by phenytoin, phenobarbital; increased by erythromycin, dextropropoxyphene. Alcohol disrupts carbamazepine metabolism
Gabapentin	▶ Unknown mechanism: despite the name, not GABAergic ▶ Not protein bound; 80% renally excreted unchanged	▶ Partial-onset and secondarily generalised seizures ▶ Start 300 mg daily, maintenance 900–3600 mg (3× daily: half-life 5–7 h)	▶ Dose-related. Drowsiness, dizziness, headache, tremor ▶ Idiosyncratic. Weight gain ▶ Teratogenicity. Insufficient human data	▶ Nil
Lamotrigine	▶ Stabilises voltage-dependent sodium channels ▶ 50% protein bound; liver metabolised	▶ Partial-onset seizures and generalised tonic-clonic seizures, some benefit to generalised absences – Monotherapy. Start 25 mg daily (introduce slowly avoiding rash), maintenance 200–600 mg. – Adding lamotrigine to valproate, start 25 mg alternate days, maintenance 100–150 mg. – Adding lamotrigine to enzyme inducers, start 50 mg daily, maintenance 300–600 mg. ▶ Frequency: 1–2× daily (half-life 12–60 h)	▶ Dose-related. Drowsiness, headache, diplopia. ▶ Idiosyncratic. Rash (10%) sometimes severe in children (Stevens-Johnson syndrome), especially with valproate ▶ Teratogenicity. Major malformations low risk (fig), but dose-related. May include oral clefts	▶ Effect on others. Increases carbamazepine epoxide (dizziness, diplopia). Lowers contraceptive pill level (uncertain mechanism) ▶ Effect of others. Valproate inhibits lamotrigine's metabolism, halving its necessary dose. Contraceptive pill lowers lamotrigine levels
Levetiracetam	▶ Binds to SV2A synaptic vesicle protein ▶ Not protein bound; not liver metabolised; renally excreted largely unchanged	▶ Partial-onset and generalised tonic-clonic seizures, myoclonus and possibly absences ▶ Start 250 mg daily; maintenance 750–4000 mg ▶ Frequency: 1–2× daily (half life 6–8 h)	▶ Dose related. Tiredness, mood change ▶ Idiosyncratic. Weight loss ▶ Teratogenicity. Insufficient data; preliminary data encouraging	▶ Nil known
Oxcarbazepine	▶ Stabilises voltage-dependent sodium channels (keto-analogue of carbamazepine) ▶ 40% protein bound, liver metabolised to 10-monohydroxy-oxcarbazepine (pharmacologically active)	▶ Partial-onset and generalised tonic-clonic seizures ▶ Maintenance 900–2400 mg daily ▶ Frequency: 2× daily (half-life 8–10 h). ▶ Elderly on diuretics, check electrolytes beforehand. Seizures persisting despite oxcarbazepine, check serum sodium	▶ Dose-related. Tiredness. ▶ Idiosyncratic. Rash, hyponatraemia, especially elderly or on diuretics ▶ Teratogenicity. Insufficient human data	▶ Effect on others. Lowers contraceptive pill level ▶ Effect of others. Nil major
Phenobarbital	▶ Enhances GABA transmission and probably stabilises voltage-dependent sodium channels ▶ 50% protein bound and liver metabolised	▶ Partial-onset and generalised seizures, including absences ▶ Start 60 mg daily, maintenance 60–180 mg daily (1–2× daily: half-life 60 h) ▶ Withdraw only slowly: no faster than 25% every 6 weeks	▶ Dose related. Drowsiness, cognition, behaviour changes in up to 50% ▶ Idiosyncratic. Reduced bone mineral density ▶ Teratogenicity. Insufficient human data despite extensive use	▶ Effect on others. Reduces other liver-metabolised drugs, including contraceptive pill. ▶ Effect of others. Valproate induces excess sedation.
Phenytoin	▶ Stabilises voltage-dependent sodium channels ▶ 90% protein bound; liver metabolised with "saturation" kinetics	▶ Partial-onset and generalised tonic-clonic seizures. Also, with rapid effect, intravenously for acute symptomatic seizures and status epilepticus ▶ Start 200 mg daily; maintenance 200–500 mg ▶ Frequency: 1–2× daily (half-life 7–42 h). Emergency loading, eg, status, 20 mg/kg by slow infusion (filtered and under ECG control) ▶ Blood levels needed because of difficult kinetics (therapeutic range 40–80 μmol/l (10–20 μg/ml)). Adjust in 25–50 mg steps according to response, adverse effects or blood levels	▶ Dose-related: unsteadiness, cerebellar ataxia, nystagmus, involuntary movements ▶ Idiosyncratic. Rashes, lymphadenopathy, cosmetic (coarsened features, gum hypertrophy, hirsutism, acne), folate and vitamin D deficiency (osteomalacia: check bone density in elderly on long-term phenytoin), cerebellar ataxia, peripheral neuropathy ▶ Teratogenicity. Despite teratogenic potential, relatively low risk in monotherapy (fig)	▶ Effect on others. Enzyme induction lowers many medications—for example, carbamazepine, lamotrigine, oral contraceptive pill ▶ Effect of others – Liver metabolised drugs (for example, isoniazid, rifampicin, carbamazepine) impairing phenytoin metabolism increasing its levels – Protein-bound drugs (for example, aspirin, valproate) displace phenytoin from protein binding sites, lowering its total levels – Enzyme inhibitors (for example, valproate) increase phenytoin blood levels (note valproate's opposite effects: no net therapeutic effect)

Continued

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Table 1 Continued

Drug	Mechanisms and kinetics	Prescribing	Adverse effects	Interactions
Pregabalin	► Binds to voltage-gated calcium channels; reduces glutamate release ► Not protein bound; no liver metabolism	► Partial-onset and generalised tonic-clonic seizures ► Dose. Start 150 mg daily; maintenance 150–600 mg ► Frequency: 1–2× daily (half-life 6 h)	► Dose related. Somnolence, dizziness, ataxia ► Idiosyncratic. Weight gain. ► Teratogenicity. Insufficient human data	► Nil
Tiagabine	► Inhibits neuronal GABA uptake ► 95% protein bound; liver metabolised	► Partial-onset seizures, generalised tonic-clonic seizures ► Monotherapy: start 15 mg daily; maintenance 30–45 mg (with enzyme inducers, up to 60 mg) ► Frequency: 2× daily (half-life 5–9 h); 3× daily with enzyme-inducers (half-life 3 h)	► Dose-related. Dizziness, sedation, headache ► Teratogenicity. Insufficient human data	► Effect on others. Nil significant ► Effect of others. Enzyme-inducers (for example, carbamazepine) accelerate its metabolism, reducing half-life to 2–3 h
Topiramate	► Blocks voltage-gated sodium channels, AMPA and kainate receptors, carbonic anhydrase; enhances GABA ► 15% protein bound; liver metabolised	► Partial-onset and generalised tonic-clonic seizures, absences and myoclonus ► Start 15 mg daily, maintenance 100–600 mg ► Frequency: 1–2× daily (half-life 19–25 h)	► Dose-related. Sleepiness, slowed thought and speed of articulation, paraesthesiae ► Idiosyncratic. Weight loss, renal calculi ► Teratogenicity. Insufficient human data	► Effect on others. Increases contraceptive pill clearance ► Effect of others. Nil significant
Valproic acid	► Raises GABA levels (uncertain mechanism) ► 90% protein bound, liver metabolised	► Partial onset seizures, primary and secondarily generalised seizures (including myoclonus and absence) ► Start 200–500 mg daily; maintenance 500–3000 mg ► Frequency. 1–2× daily (half-life 12–17 h, therapeutic effect longer)	► Dose-related: nausea, vomiting, diarrhoea, tremor, irritability, poor sleep, confusion ► Idiosyncratic. Hair loss, weight gain, polycystic ovaries, hyperammonaemia (occult urea cycle disorders), hepatotoxicity (especially young children with Alpers' disease (1 in 50 000)) ► Teratogenicity. Spina bifida aperta in 2% (fig); concern over "fetal valproate syndrome" and possible neuro-developmental delay	► Effect on others – Enzyme inhibition elevates lamotrigine (care in combination), carbamazepine 10,11-epoxide (adverse effects at "therapeutic" level), phenobarbital, and alcohol (increased sedation) – Protein binding displacement raises other medications' free level (for example, warfarin) ► Effect of others – Enzyme inducing drugs lower total valproate levels (for example, carbamazepine, phenytoin) – Protein bound drugs displace and increase free valproate levels (for example, aspirin)
Zonisamide	► Blocks voltage-gated sodium channels, T-type calcium currents, glutamate transmission, carbonic anhydrase ► 50% protein bound; liver metabolised	► Partial-onset, generalised tonic-clonic seizures, some effect in generalised seizures including progressive myoclonic epilepsy ► Dose. Start 50 mg daily; maintenance 200–600 mg ► Frequency: Once daily (half-life 49–69 h)	► Dose related. Somnolence, ataxia, dizziness ► Idiosyncratic. Rash, renal calculi, heat stroke ► Teratogenicity. Insufficient human data	► Effect on others. Probably increases contraceptive clearance ► Effect of others. Nil significant

excess alcohol lowers seizure threshold through poor sleep quality; alcohol withdrawal is a common cause of provoked seizures. Valproate inhibits alcohol metabolism, promoting intoxication.

- **Flashing lights** are worth mentioning to all epilepsy patients, because so many erroneously believe they must avoid them.
- **Folate**. Despite the lack of evidence of benefit in humans, we still advise women on AEDs who may become pregnant (for example, not on the contraceptive pill) to take folate 5 mg daily.
- **Disability benefit** presents eligibility difficulties because the seizures are intermittent and variable. The payments are not inconsiderable

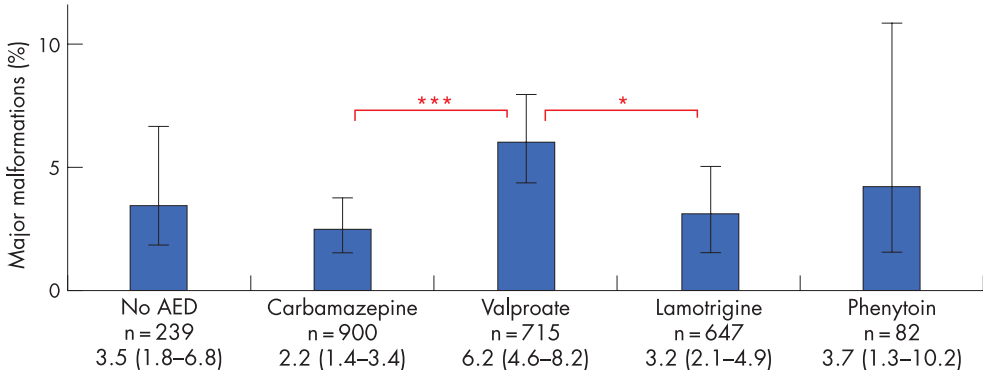

Figure 1 Major malformation risk (mean ± 95% confidence interval) from the UK Epilepsy and Pregnancy Register (***p<0.001; *p<0.05).

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and may present a conflict of interest for many people with epilepsy.

- **Sudden unexplained death in epilepsy (SUDEP)**. Although discussing such a sensitive issue is difficult, saying nothing risks patients later resenting the apparent concealment. SUDEP can be discussed positively, emphasising its rarity, and the possible steps in avoidance including taking AEDs regularly, and avoiding excess alcohol.
- **Genetics**. Several monogenic epilepsies have been identified but for practical purposes there are as yet no specific epilepsy genetic tests available.

Surgery

Lesional epilepsy surgery

This is the removal of a clearly demonstrated lesion—for example, hippocampal sclerosis, ganglioglioma. Following hippocampal sclerosis surgery, up to 80% may become seizure-free, half of these withdrawing AEDs. The results are less good for cortical dysplasia and less good again for patients with normal imaging. Although the surgery itself is relatively straightforward, it requires prolonged pre-surgical workup to establish firstly if the lesion is definitely the epileptogenic focus and, secondly, if it is safe to remove (memory and speech).

Non-lesional epilepsy surgery

These operations aim to limit seizure discharge spread.

- **Corpus callosotomy** prevents bilateral spread of intractable generalised seizures, particularly atonic seizures with falls.
- **Hemispherectomy** can be surprisingly beneficial in children with pre- or perinatal onset of hemiplegia and refractory seizures.
- **Multiple subpial transections** interfere with horizontal transmission within the cortex through multiple cortex-deep cuts to isolate blocks of cortex.

Radiosurgery

"Gamma knife" surgery used for small arteriovenous malformations, small tumours, metastases and sometimes for hippocampal sclerosis.

Vagus nerve stimulation

The mechanism is unknown but it appears as effective as adding a new AED: 30–50% obtain >50% seizure reduction. Although invasive it gives 100% compliance without drug interactions or sedative effects. Adverse effects include implantation site pain, hoarseness and swallowing problems.

CONCLUSIONS

- Epilepsy is a common, complex and often chronic condition affecting all ages.
- Diagnosis can be surprisingly challenging, and relies not on tests but on a full and accurate history.
- Management encompasses lifestyle choices, AEDs and surgery, with special considerations for certain client groups.
- Many people with epilepsy can now realistically expect seizure freedom without medication adverse effects.
- Greater clinical openness together with widely available information has facilitated improving knowledge and awareness about epilepsy among patients, their families and carers.
- People with epilepsy can now expect to be better integrated into home, working and community life, and ultimately lead fuller, more independent, and more active lives than previously thought possible.

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