Adult epilepsy

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The epilepsies are one of the most common serious brain disorders, can occur at all ages, and have many possible presentations and causes. Although incidence in childhood has fallen over the past three decades in developed countries, this reduction is matched by an increase in elderly people. Monogenic Mendelian epilepsies are rare. A clinical syndrome often has multiple possible genetic causes, and conversely, different mutations in one gene can lead to various epileptic syndromes. Most common epilepsies, however, are probably complex traits with environmental effects acting on inherited susceptibility, mediated by common variation in particular genes. Diagnosis of epilepsy remains clinical, and neurophysiological investigations assist with diagnosis of the syndrome. Brain imaging is making great progress in identifying the structural and functional causes and consequences of the epilepsies. Current antiepileptic drugs suppress seizures without influencing the underlying tendency to generate seizures, and are effective in 60–70% of individuals. Pharmacogenetic studies hold the promise of being able to better individualise treatment for each patient, with maximum possibility of benefit and minimum risk of adverse effects. For people with refractory focal epilepsy, neurosurgical resection offers the possibility of a life-changing cure. Potential new treatments include precise prediction of seizures and focal therapy with drug delivery, neural stimulation, and biological grafts.

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Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and epileptogenesis is the development of a neuronal network in which spontaneous seizures occur. Epilepsy affects the whole age range from neonates to elderly people, and has varied causes and manifestations, with many distinct seizure types, several identifiable syndromes, but also much that is poorly classified. There are very many comorbidities that complicate assessment and treatment planning, including learning disabilities, fixed neurological deficits, progressive conditions, psychological and psychiatric problems, and, particularly in the older age group, concomitant medical conditions.

Classification of epileptic seizures and syndromes is continually evolving. The present proposed classification is across five axes that consider seizure types, focal or generalised seizure onset, the syndrome, causation, and associated deficits.[1] Here, we have defined individuals aged 16 years and older as adults. The UK National Institute for Health and Clinical Excellence (NICE) produced in October 2004 detailed evidence-based guidelines[2] for the clinical management of individuals with epilepsy (panel). Other guidelines include those of the American Academy of Neurology and the Scottish Intercollegiate Guidelines Network.

Stigma and prejudice mark epilepsy out from other neurological conditions. The past decade has seen considerable progress in epilepsy research, and improvement in public understanding. Much, however, remains to be done, especially for people for whom drugs are ineffective. An important issue that needs urgent attention is the fact that most people with epilepsy live in resource-poor countries where the management of epilepsy is inconsistent. There is a great diagnostic gap in large parts of the world because there are too few trained personnel and medical facilities. The WHO-led Global Campaign Against Epilepsy with the active support of the International League Against Epilepsy and International

Panel: NICE epilepsy guidelines key points[2]

- Diagnosis should be made urgently by a specialist with an interest in epilepsy
- EEG used to support diagnosis when the clinical history suggests it
- MRI should be used in people who develop epilepsy as adults, in whom focal onset is suspected, or in whom seizures persist
- Seizure types and epilepsy syndrome, cause, and comorbidity should be determined
- Initiation of appropriate treatment recommended by a specialist
- Treatment individualised according to the seizure type, epilepsy syndrome, comedication and comorbidity, individual's lifestyle, and personal preferences
- Individual with epilepsy, and their family, carers, or both, participate in all decisions about their care, taking into account any specific need
- Comprehensive care plans agreed
- Comprehensive provision of information about all aspects of condition
- Regular structured review at least once a year
- Referral back to secondary or tertiary care if
  - Epilepsy inadequately controlled
  - Pregnancy considered or pregnant
  - Antiepileptic drug withdrawal considered

Search strategy and selection criteria

We searched PubMed for articles from 2002, with the keywords "epilep*", "EEG", "MRI", "seizure prediction", "SUDEP", "antiepileptic drug", "gene*", "surgery", and "mechanisms". We also cite occasional earlier articles and reviews, where these are particularly relevant.

For **UK National Institute for Health and Clinical Excellence Guidelines** see http://www.nice.org.uk

For **American Academy of Neurology guidelines** see http://www.guideline.gov

For **Scottish Intercollegiate Guidelines Network** see http://www.sign.ac.uk

For **the Global Campaign Against Epilepsy** see http://www.who.int/mental_health/management/globalepilepsycampaign

Bureau for Epilepsy (the two major international non-governmental organisations in epilepsy) is seeking to address these issues.[3,4] Additionally, there is a large treatment gap in resource-poor countries, and worldwide, less than 20% of people with the disorder are estimated to be treated at any time.[5,6] However, resolving these difficulties will require tremendous effort and will take time to achieve. Most of what we discuss here relates to diagnosis and treatment of epilepsy as seen in the developed world. We hope that before long, the same standards will be achieved in resource-poor countries.

Epidemiology

The incidence of epilepsy in developed countries is around 50 per 100 000 people per year, and is higher in infants and elderly people.[7–9] Less wealthy people show a higher incidence, for unknown reasons.[10] Poor sanitation, inadequate health delivery systems, and a higher risk of brain infections and infestations could contribute to a higher incidence—usually above 100 per 100 000 people per year—in resource-poor countries where most people with epilepsy usually do not receive treatment.[8,11] Childhood incidence has fallen over the past three decades in developed countries, which could be a result of adoption of healthier lifestyles by expectant mothers, improved perinatal care, and immunisation programmes. A parallel rise in incidence in elderly people could be related to improved survival in people with cerebrovascular disease and cerebral degeneration.[8,12]

The prevalence of epilepsy is between 4 and 10 per 1000 people per year.[8,9] A few (typically small) studies from isolated geographical areas with unique genetic or environmental factors[8] have shown higher rates. Lifetime prevalence rates are much higher than rates of active epilepsy, even in resource-poor countries where most people do not have access to antiepileptics.[8] This difference is mainly explained by the cessation of seizures in most people who develop the disorder, but also partly by increased mortality in epilepsy.[13,14]

Risk factors vary with age and geographical location. Epilepsy associated with head trauma, central nervous system infections, and tumours occurs at any age. Cerebrovascular disease is the most common risk factor in people older than 60 years.[15] Endemic parasitic diseases such as falciparum malaria and neurocysticercosis are probably the most common preventable risks for epilepsy worldwide.[11,16–20] Recently, toxocariasis and onchocerciasis have been suggested as important risk factors.[21,22] Susceptibility to epilepsy could be partly genetically determined. The complex interplay between genetic and environmental factors might underlie our incomplete understanding of the population dynamics of the disorder.[11] Additionally, some epileptic syndromes evolve over time. Two examples of this evolution are infantile spasms progressing to Lennox-Gastaut syndrome (an especially severe form of epilepsy), and the occurrence of febrile convulsions in an infant leading to the later development of medial temporal lobe epilepsy. From an epidemiological or biological point of view, however, the mechanisms of progression have not yet been fully elucidated and genetic factors are likely to have a role.

In developed countries, more than 60% of patients achieve long-term remission, usually within 5 years of diagnosis; the possibility of remission decreases the longer the epilepsy is active.[8] Predictors of good outcome include earlier age of onset, fewer early seizures,[23,24] and early response to drug treatment.[25] In any individual, outcome and response to treatment can be inherent to either the condition or to the individual, and seizure control in some can be difficult from the outset.[8,26] In developed countries, the overall good prognosis is often attributed to the widespread use of antiepileptic drugs. In resource-poor countries lacking such drugs, however, many patients enter long-term remission, lending support to the suggestion that prognosis is dependent on the cause of the epilepsy and not on drug treatment.[26] Up to a third of people having seizures develop chronic epilepsy.[26] However, up to 20% of patients referred to clinics with refractory epilepsy might have been misdiagnosed, and many more could be helped by optimum treatment.[27] People with chronic epilepsy also have an increased risk of comorbid conditions, including cardiovascular and cerebrovascular disorders, gastrointestinal disorders, fractures, pneumonia, chronic lung diseases, and diabetes.[28]

Mortality

People with epilepsy have an increased risk of premature death.[29] Symptomatic epilepsy can reduce life expectancy by up to 18 years.[30] Sudden death, trauma, suicide, pneumonia, and status epilepticus are more common in people who have epilepsy than those without the disorder.[31] Little is known about mortality in resource-poor countries, although circumstantial evidence suggests that it is higher than in developed countries, helping to explain the discrepancy between the higher incidence and lower prevalence of active epilepsy in poor countries.[8]

Sudden unexpected death in epilepsy is thought to account for at least 500 deaths per year in the UK, and is not fully explained.[32] In people with refractory epilepsy attending specialist clinics, the yearly rate is one per 200. The highest risk is in male teenagers and young adults with convulsive seizures.[33] High seizure frequency and severity are risk factors, and in the highest risk group (ie, those who have been considered for surgery but declined)—the yearly rate is one per 75 individuals.[34] Sleeping unattended is another risk factor.[35,36] The pathophysiological causes of sudden unexplained death in epilepsy is unknown, but cardiac arrhythmias—in particular asystole secondary to seizures—have been noted in monitoring studies and might only arise with occasional seizures (figure 1).[37] Further long-term electrocardiogram (ECG) monitoring studies are needed to identify characteristics that carry a high risk of asystole and indicate prophylactic cardiac pacing.

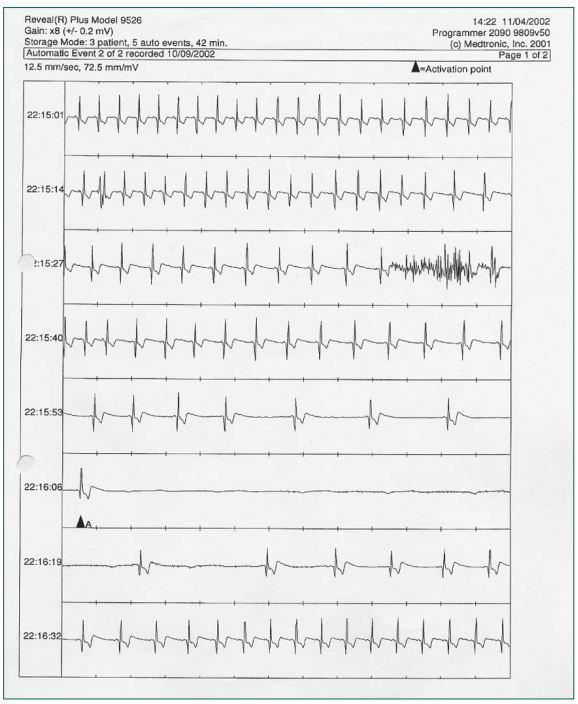

Figure 1: **Electrocardiogram showing asystole resulting from temporal lobe seizure[37]**

Pathophysiology

An epileptic seizure is a transient occurrence of signs, or symptoms, or both, due to abnormal excessive or synchronous neuronal activity in the brain.[38] Brief synchronous activity of a group of neurons leads to the interictal spike, which has a duration of less than 70 ms and is distinct from a seizure.[39] Indeed, the site of interictal spiking can be separate from the zone of seizure onset.

An early view that disruption of the normal balance between excitation and inhibition in the brain results in seizure generation is now thought to be an over-simplification. The function of the brain depends on cooperation between disparate networks that is probably mediated through oscillations within these networks. Cortical networks generate oscillations, for which inhibitory neurons,[40] neuronal communication (eg, synaptic transmission), and intrinsic neuronal properties (eg, the ability of a neuron to maintain burst firing) are crucial. The occurrence of epileptic activity might be an emergent property of such oscillatory networks.[41] Transition from normal to epileptiform behaviour is probably caused by greater spread and neuronal recruitment secondary to a combination of enhanced connectivity, enhanced excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties. In studies in man the electro-encephalogram (EEG) becomes less chaotic within large areas of cortex before a seizure, suggesting that widespread synchronisation is taking place.[42]

In focal epilepsies, focal functional disruption—often due to focal pathological changes (eg, tumour), or rarely to a genetic diathesis (eg, autosomal dominant frontal lobe epilepsy)—results in seizures beginning in a localised fashion, which then spread by recruitment of other brain areas. The site of the focus and the speed and extent of spread determine the clinical manifestation of the seizure.

Generalised epilepsies result in seizures occurring throughout the cortex because of a generalised lowering of seizure threshold, and are usually genetically determined. Absence seizures are a distinct form of generalised seizure generated by thalamocortical loops (figure 2).[43] Absences were originally believed to be generated subcortically, by thalamic neurons driving recruitment of neocortical neurons. However, paroxysmal oscillations within thalamocortical loops in absence seizures in rats seem to originate in the somatosensory cortex rather than the thalamus, with synchronisation mediated by rapid intracortical propagation of seizure activity.[44] Together with observations of subtle cortical structural abnormalities in some patients with absence seizures,[45] and the potential of focal pathological change in the medial frontal lobe to generate absence-like seizures, the distinction between focal and generalised epilepsies has become blurred.

Genetic basis and contribution

Genetic variation can determine the causes, susceptibility, mechanisms, syndrome, treatment response, prognosis, and consequences of the epilepsies to varying degrees. Part of the promise of genetics lies in its power to relate these characteristics of the overall clinical presentation of the individual patient. There has been considerable progress in this area.[46,47] Several monogenic Mendelian epilepsies are known, but are generally rare and account for few cases. There can be variation in the genetic causes of a clinically homogeneous syndrome, such as juvenile myoclonic epilepsy,[48,49] and, conversely, different mutations in a single gene can cause various epilepsy syndromes.

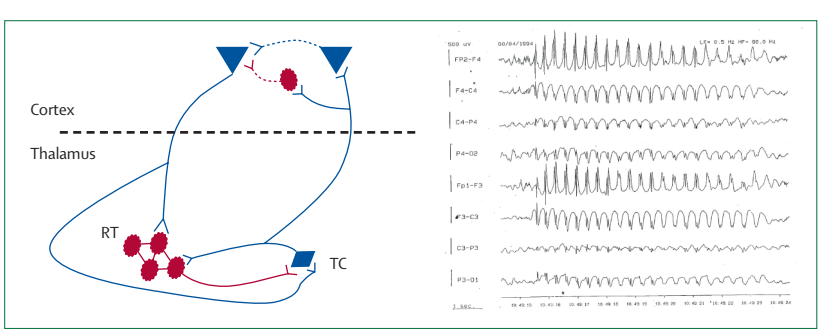

Figure 2: **Possible mechanism of generation of spike-wave discharges (absences)**
Burst firing of cortical neurons leads to recruitment of reticular thalamic (RT) neuronal network. Activation of low-threshold calcium currents results in burst firing of RT network, releasing γ aminobutyric acid (GABA) onto thalamocortical (TC) neurons, which are hyperpolarised through activation of $GABA_B$ and $GABA_A$ receptors. This hyperpolarisation results in deinactivation of T type calcium channels. On repolarisation, these calcium channels open, resulting in a burst of action potentials from TC neurons that then drives the cortical neurons (left). In this way the cycle continues generating the spike-wave discharges seen on scalp EEG (right).
Red=inhibitory GABAergic neurons. Blue=excitatory glutamatergic neurons.

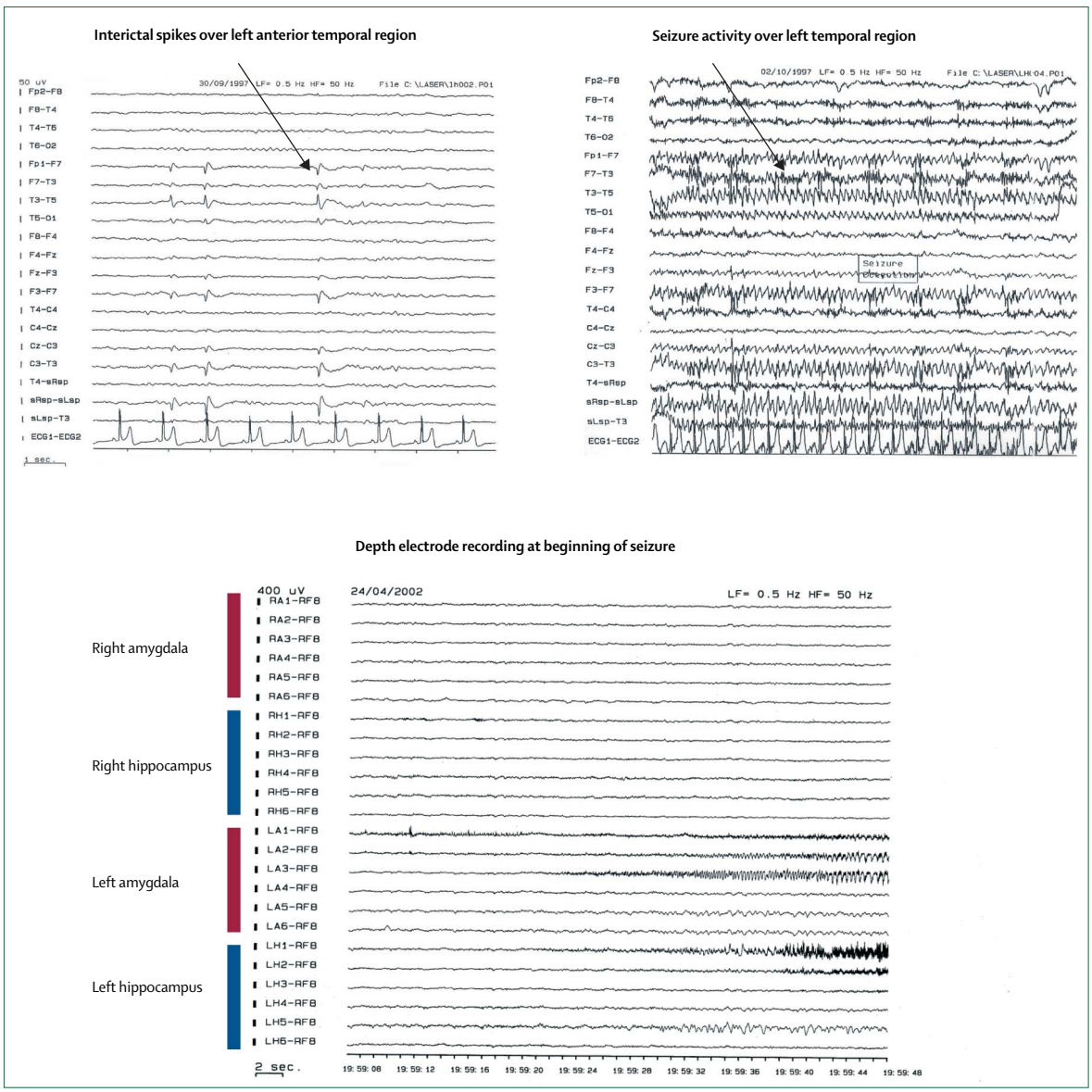

Figure 3: **EEG in temporal lobe epilepsy**

Upper=scalp EEG recordings: left, interictal EEG demonstrating anterior temporal spikes; right, rhythmic activity over left temporal region during seizure. Lower=EEG recording from intracranial electrodes (placed in right amygdala and hippocampus and left amygdala and hippocampus) showing fast activity in left amygdala and hippocampus at beginning of temporal lobe seizure.

Thus, different mutations in the gene *SCN1A*, which encodes a neuronal sodium channel α subunit, underlie a range of epilepsies, from the severe myoclonic epilepsy of infancy to the usually more benign generalised epilepsy with febrile seizures plus,[50,51] which, conversely, might result from mutations in other genes.[52,53]

The present belief that most common epilepsies are complex traits with environmental effects acting on a background of multigenic or oligogenic susceptibility, mediated by common genetic variation—especially single nucleotide polymorphisms—is largely based on genetic epidemiological studies.[54] Idiopathic generalised epilepsies are emerging as an example of such complex disease causation.[55,56] Relevant genetic variation is usually identified by population genetic association studies of large groupings of well characterised patients whose genotypes are related to their phenotypes. Many such studies of susceptibility and other phenotypic features have been published, but very few have been replicated.[57,58] Evolving methods and larger collaborative studies will reveal single nucleotide polymorphisms and other common genetic variants that confer disease susceptibility.[59]

Diagnosis and investigation

The diagnosis of epilepsy remains clinical and is based on probability after assessment of the whole individual.

Misdiagnosis is potentially very damaging. The differential diagnosis must therefore always be carefully considered. In some cases the diagnosis of epilepsy syndrome or seizure types is incorrect, or the events are not due to epilepsy at all, but instead have their basis in a cardiac, psychological, psychiatric, or metabolic disturbance. Such non-epileptic seizures are important to identify since they have distinct causes, treatments, and risks, including the results of inappropriate use of antiepileptic drugs, especially in an emergency setting, and withholding of appropriate therapy.[27]

Sometimes, diagnosis of epilepsy has to be delayed while witness accounts are sought. Video recordings filmed out of hospital are increasingly accessible and form a very useful adjunct, especially when seizures are infrequent. Other investigation will only rarely affect the actual diagnosis of epilepsy, although it can be crucial for establishing the syndromic diagnosis and cause. Good practice is to do an ECG for everyone presenting with possible seizures, especially if the events include loss of awareness and falls. A proportion of such episodes will be due to cardiac arrhythmia—indicated, for example, by a prolonged QT interval. In cases of diagnostic uncertainty a full cardiac assessment is appropriate and could reveal a primary cardiovascular cause. For infrequent events with a possible cardiac cause, an implanted ECG loop recorder is an essential diagnostic aid, often leading to specific and effective therapy.[60]

In clinical practice, the hallmark of epilepsy is interictal epileptic activity: spikes, sharp waves, and spike-wave discharges (figure 3). The integration of the clinical description of the seizures, the age and comorbidities of the patient, the EEG patterns, and brain imaging lead to a syndromic diagnosis that conveys prognostic information. Prolonged digital ambulatory and video EEG provide greater temporal samples than a standard 30 min EEG and, if seizures are frequent, the realistic possibility of direct observation and recording of habitual seizures. Such information is invaluable in the event of diagnostic uncertainty and if surgical treatment is considered.[61]

The mainstay of elective brain imaging is MRI, which is becoming increasingly available. The quality of MRI has improved greatly over the past decade. There remains a gulf between the sensitivity and specificity of optimum imaging as obtained at a centre of excellence, and non-specialised routine brain MRI.[62,63] Widespread adoption of agreed imaging protocols[64,65] would be an important step forward. In resource-poor countries, access to MRI can be restricted or non-existent. In this situation, CT might be more accessible and can be used to assess gross pathological changes, but cannot identify most of the subtle changes that commonly underlie epilepsy. MRI is especially important in individuals with refractory partial seizures who would be potential candidates for surgical treatment, and in those with progressive neurological or psychological deficits.[64,65] The sensitivity of MRI in detection of subtle changes that could underlie refractory focal epilepsies, such as focal cortical dysplasia, is improving with new MRI acquisition sequences (figure 4). Diffusion tensor imaging,[66] magnetisation transfer imaging,[67] and T2 mapping[68,69] show promise. Tractography can visualise white-matter tracts including connections of eloquent areas[70] and can be used to reduce the risks of surgery[71] (figure 5).

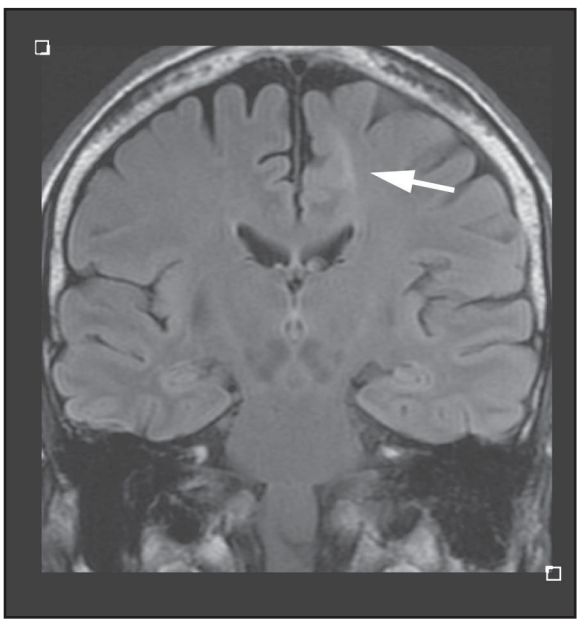

Figure 4: **Focal cortical dysplasia**
Arrow=cortical dysplasia in medial left frontal lobe, extending to superior border of frontal horn (left side of brain is on right side of image).

Automated data analysis is becoming an important adjunct to visual interpretation.[72,73] Voxel-based analysis can identify subtle changes in the neocortex over time

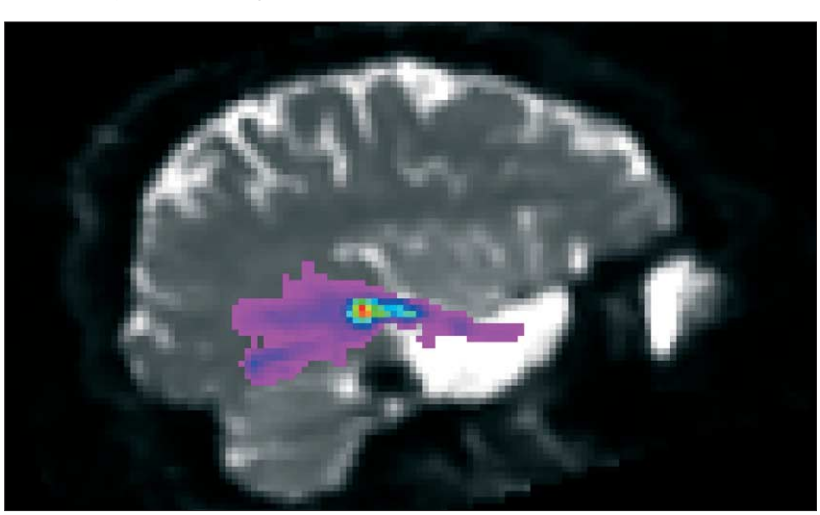

Figure 5: **Tractography outlining the right optic radiation, superimposed on a sagittal MRI scan after right anterior temporal lobe resection**
A superior left quadrantic visual field defect was noted after surgery, caused by resection affecting anterior part (Meyer's loop) of right optic radiation.

that are not evident on visual inspection.[74] In some selected patients with temporal lobe epilepsy serial studies have shown a reduction in hippocampal volume with time,[75,76] but this is a rare finding.[74] There is an increased risk of focal and diffuse neocortical atrophy developing in all epilepsies, but considerable heterogeneity exists between patients.[74]

Functional MRI (fMRI) of the blood–oxygen-level-dependent (BOLD) contrast is increasingly used to lateralise language before surgery[77,78] and can predict deficits after temporal lobe resection.[79,80] fMRI is removing the need for the carotid amytal test, but caution is required because discrepancies can arise.[81] Impairment of memory after temporal lobe resection, particularly of verbal memory after left anterior temporal lobe resection, is a concern. fMRI can visualise the functional anatomy of memory tasks[82–85] and hence the probable effects of surgery on individuals, assisting decision-making and planning of surgery. The simultaneous recording of EEG and fMRI can visualise the BOLD response to interictal epileptic activity. This emerging technique could assist in identifying targets for surgical treatment.[86,87]

Functional imaging of the brain with isotopes has a clinical role in assessment of suitability for epilepsy surgery. Objective analyses of single photon emission computed tomography (SPECT) studies of ictal, postictal, and interictal blood flow have shown focal ictal hyperperfusion with surrounding hypoperfusion, followed by hypoperfusion in the focus and then return to the interictal state. SPECT could be useful in identification of a possible epileptic focus, particularly when structural imaging is unremarkable, to generate hypotheses that can be tested with intracranial EEG studies,[88] and indicate areas involved in the spread of seizures from the medial temporal lobe.[89] PET imaging with fluorodeoxyglucose might show an area of hypometabolism that, if MRI is normal, could suggest the possible site of seizure onset, which could then be tested with intracranial EEG.[90]

Flumazenil binding to the central benzodiazepine receptor complex with $GABA_A$ might be abnormal in a more restricted area than is fluorodeoxyglucose binding, and might provide data that are useful to presurgical assessment when MRI is not definitive.[91] Other tracers that explore the pathogenesis of epilepsies and which could have localising value include alphamethyl tryptophan[92] and 5HT 1A.[93]

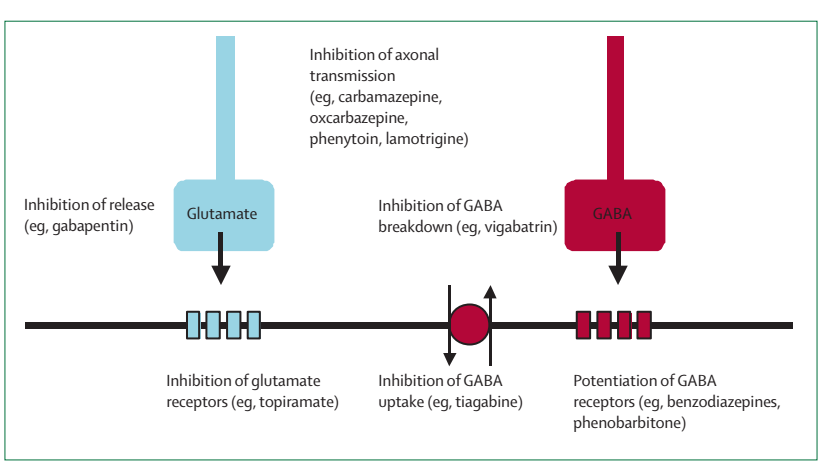

Figure 6: **Main targets of antiepileptic drugs**

Drug treatment

Antiepileptic drugs are the mainstay of epilepsy treatment. Non-pharmacological treatments are feasible only in a few selected cases and usually after antiepileptics have failed. Non-pharmacological options include curative surgery, palliative surgical procedures, and the ketogenic diet. The main indications for the ketogenic diet are severe forms of drug-resistant epilepsy in paediatric practice.[94,95] Overall, antiepileptic drugs are effective in 60–70% of individuals. The aim of antiepileptic treatment is to control seizures as quickly as possible without adverse effects.[96] Improved seizure control is likely to reduce morbidity and premature mortality associated with continuing seizures, especially convulsive attacks.[13] Further, seizure remission is the major determinant of good quality of life.[97]

Drugs for epilepsy increase inhibition, decrease excitation, or prevent aberrant burst-firing of neurons. Some were discovered empirically through screening programmes of induced seizures in animals without epilepsy. The mechanisms of action are not fully understood and many antiepileptic drugs have multiple actions. The principal mechanisms of present drugs are thought to be enhancement of the inhibitory GABAergic system (eg, benzodiazepines, barbiturates, tiagabine, vigabatrin) or use-dependent block of sodium channels (eg, carbamazepine, oxcarbazepine, lamotrigine, and phenytoin; see figure 6).[98] Even within these groups, drugs can have very different modes of action. Benzodiazepines bind to $GABA_A$ receptors, potentiate the response to GABA, and are used in generalised and partial seizures. Tiagabine, on the other hand, inhibits GABA uptake, potentiating $GABA_A$ and $GABA_B$ receptor responses, which hyperpolarise and decrease the excitability of neurons.[98] Although this process suppresses partial seizures, hyperpolarisation of thalamocortical cells can result in exacerbation of absences.

Drugs that specifically target glutamate receptors have had little success because of unacceptable side-effects, but some useful drugs (eg, topiramate) might affect glutamatergic transmission. Antiepileptic drugs can act on ion channels that affect neuronal excitability. Calcium channels are crucial for cell excitability and also for neurotransmitter release. Ethosuximide might target T type calcium channels, which would explain its specificity for absence seizures. Other drugs (eg, gabapentin, pregabalin) target presynaptic calcium channels, thus inhibiting neurotransmitter release. Modulation of neurotransmitter release might be an effective way of modifying network excitability. Levetiracetam binds

	Putative modes of action	Routes of elimination and metabolites	Usual starting dose in adults	Usual daily maintenance dose in adolescent and adults	Main safety issues or concerns
Acetazolamide (1952)	Carbonic anhydrase inhibition	Renally excreted	250 mg	500–1000 mg	Idiosyncratic rash; rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; aplastic anaemia
Carbamazepine (1963)	Sodium-channel inhibition	Hepatic metabolism; active metabolite	100–200 mg	400–1800 mg	Idiosyncratic reactions; rarely Stevens-Johnson syndrome; aplastic anaemia, hepatotoxicity
Clobazam (1986)	GABA augmentation	Hepatic metabolism; active metabolite	10 mg	10–30 mg	Rarely idiosyncratic rash
Clonazepam (1975)	GABA augmentation	Hepatic metabolism	0·5 mg	1–6 mg	Rarely idiosyncratic rash, thrombocytopenia
Diazepam (1965)	GABA augmentation	Hepatic metabolism; active metabolite	10–20 mg	N/A	Respiratory depression
Ethosuximide (1953)	Calcium-channel modification	Hepatic metabolism; 25% excreted unchanged	250 mg	500–1500 mg	Rarely idiosyncratic rash, Stevens-Johnson syndrome, aplastic anaemia
Felbamate (1993)	Glutamate reduction	Hepatic metabolism; active metabolites	400 mg	1800–3600 mg	Hepatic failure, aplastic anaemia
Gabapentin (1993)	Calcium-channel modulation	Not metabolised, urinary excretion unchanged	300 mg	1800–3600 mg	Paradoxical increase in seizures
Lamotrigine (1991)	Sodium-channel inhibition; glutamate reduction	Hepatic metabolism by glucuronidation	50 mg (10 mg if taking valproate)	100–400 mg	Idiosyncratic rashes, rarely Stevens-Johnson syndrome, Toxic epidermal necrolysis, liver failure, aplastic anaemia, multiorgan failure
Levetiracetam (1999)	Synaptic vesicle protein modulation	Urinary excretion	250 mg	750–3000 mg	Behavioural problems
Lorazepam (1972)	GABA augmentation	Hepatic metabolism	2–4 mg	N/A	Respiratory depression
Phenobarbital (1912)	GABA augmentation	Hepatic metabolism; 25% excreted unchanged	30 mg	30–180 mg	Idisyncratic rash; rarely toxic epidermal necrolysis; hepatotoxicity; osteomalacia; Dupuytren's contracture
Phenytoin (1938)	Sodium-channel inhibition	Saturable hepatic metabolism	200 mg	200–400 mg	Idiosyncratic rash; rarely pseudolymphoma; peripheral neuropathy; Stevens-Johnson syndrome; Dupuytren's contracture; hepatotoxicity; osteomalacia
Pregabalin (2004)	Calcium-channel modulation	Not metabolised, excreted unchanged	50 mg	100–600 mg	Weight gain; rarely increased seizures
Primidone (1952)	GABA augmentation	Hepatic metabolism	125 mg	500–1500 mg	Idiosyncratic rash; rarely agranulocytosis; thrombocytopenia; lupus-like syndrome
Oxcarbazepine (1990)	Sodium-channel inhibition	Hepatic metabolism	150–300 mg	900–2400 mg	Idiosyncratic rash; hyponatraemia
Tiagabine (1996)	GABA augmentation	Hepatic metabolism	5 mg	30–45 mg	Increased seizures; non-convulsive status
Topiramate (1995)	Glutamate reduction; sodium-channel modulation; calcium-channel modification	Mostly hepatic metabolism, with renal excretion	25 mg	75–200 mg	Weight loss; kidney stones; impaired cognition
Valproic acid (1968)	GABA augmentation	Hepatic metabolism; active metabolites	200 mg	400–2000 mg	Teratogenicity; rarely acute pancreatitis; hepatotoxicity; thrombocytopenia; encephalopathy; polycystic ovarian syndrome
Vigabatrin (1989)	GABA augmentation	Not metabolised 85% excreted unchanged	500 mg	1000–2000 mg	Visual field defects, increased seizures
Zonisamide (1990)	Calcium channel inhibition	Urinary excretion	50–100 mg	200–600 mg	Rash; rarely blood dyscrasias

GABA=γ aminobutyric acid.

Table 1: **The range of antiepileptic drugs (year of introduction) in present use**

	First-line drugs	Second-line drugs	Other drugs that can be considered	Drugs to be avoided (could worsen seizures)
Seizure type				
Generalised tonic-clonic	Carbamazepine Lamotrigine Sodium valproate Topiramate	Clobazam Levetiracetam Oxcarbazepine Zonisamide	Acetazolamide Clonazepam Phenobarbital Phenytoin	Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Clobazam Clonazepam Topiramate	..	Carbamazepine Gabapentin Oxcarbazepine Tiagabine Vigabatrin
Myoclonic	Sodium valproate Topiramate	Clobazam Clonazepam Lamotrigine Levetiracetam Piracetam Zonisamide	..	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Tonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Topiramate Zonisamide	Acetazolamide Felbamate Levetiracetam Phenobarbital Phenytoin	Carbamazepine Oxcarbazepine
Atonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Topiramate Zonisamide	Zonisamide Felbamate Levetiracetam Phenobarbital	Carbamazepine Oxcarbazepine Phenytoin
Focal with or without secondary generalisation	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate Topiramate	Clobazam Gabapentin Levetiracetam Pregabalin Tiagabine Zonisamide	Acetazolamide Clonazepam Phenobarbital Phenytoin	..
Epilepsy syndrome				
Juvenile absence epilepsy	Lamotrigine Sodium valproate	Levetiracetam Topiramate	..	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Sodium valproate Topiramate	Clobazam Clonazepam Levetiracetam Zonisamide	Acetazolamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Generalised tonic-clonic seizures only	Carbamazepine Lamotrigine Sodium valproate Topiramate	Levetiracetam Zonisamide	Acetazolamide Clobazam Clonazepam Oxcarbazepine Phenobarbital Phenytoin	Tiagabine Vigabatrin
Focal epilepsies				
Cryptogenic, symptomatic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate Topiramate	Clobazam Gabapentin Levetiracetam Phenytoin Pregabalin Tiagabine Zonisamide	Acetazolamide Clonazepam Phenobarbital	..
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Levetiracetam Topiramate	Sulthiame	..
Benign epilepsy with occipital paroxysms	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Levetiracetam Topiramate	..	..

Table 2: **Antiepileptic drug options for epileptic seizures and syndromes seen in adults**

specifically to a presynaptic vesicular protein that affects neurotransmitter release.[99] Interest is also growing in the cationic h-channel, which inhibits regenerative dendritic action potentials, since lamotrigine[100] and possibly gabapentin[101] potentiate this current.

More than 20 antiepileptic drugs are licensed worldwide (table 1). These drugs suppress the symptom (seizures) rather than modify disease process (epileptogenesis). There is no evidence that the drugs used at present change longer-term prognosis for most people.[102] In resource-poor countries, not having a reliable supply of antiepileptic drugs is a major problem, and can result in abrupt treatment withdrawal and consequent serious exacerbation of seizures. In some circumstances, prescribing a drug that is usually available (such as phenobarbital) might therefore be preferable to a newer drug whose supply might be more erratic. Although phenytoin is widely available, its effective use depends on the ability to monitor its concentration in serum. If monitoring is not feasible, the use of this agent is less attractive.

Conventionally, antiepileptic drugs are divided into old drugs and new drugs, according to whether or not they were available before the 1990s. Some of these drugs are used as first-line treatment and are selected mainly according to their clinical effectiveness for the epileptic syndrome or seizure type, and for tolerability and individual patients' circumstances.[2,96,103,104] This individualised approach to treatment is recommended in all treatment guidelines.[2–5] Existing NICE guidelines suggest a range of drugs as potential first-line treatments for the different seizure types and epilepsy syndromes that are most likely to be seen in adult practice (table 2).

New antiepileptic drugs have often been promoted as having advantages over old drugs.[105–107] There is, however, no evidence that new drugs are more effective, although they might be better tolerated, than old drugs. A comparative study of the tolerability and efficacy of two newer drugs, lamotrigine and gabapentin, with carbamazepine, showed no difference in efficacy in elderly people, but the new drugs were better tolerated than the old ones in this age group.[108] A major pragmatic clinical trial (SANAD)[109] comparing newer and older antiepileptic drugs is underway and will report within the next year.

Despite the fact that several new drugs have been licensed in recent times, the principles of epilepsy treatment have not changed much.[96] Antiepileptic treatment is still essentially empirical rather than rational. However, a rational approach to management is warranted, with a clear individualised management plan established at the earliest opportunity. For instance, women of childbearing potential should not be started on drugs that carry an increased risk of detrimental effects to a fetus unless there is no other choice.[110] In elderly people, who might be taking several drugs for other conditions, drugs that are likely to interact with others should be avoided if possible.

When should treatment should be started in people with few or infrequent seizures? A recurring issue has been whether seizures beget seizures, and therefore whether failure of early treatment leads to chronicity.[26,111] Recent evidence shows no difference in the long-term outlook for deferred versus immediate treatment,[104] which justifies the practice of waiting for further events rather than starting treatment immediately after a single seizure. Patients perceived to be at high risk of recurrence because of a structural abnormality thought to be responsible for the seizure, an abnormal EEG, a pre-existing neurological deficit, or an initial high density of seizures, should, however, still be offered antiepileptics at the first opportunity. The same holds true for those who, on understanding the risks of recurrence and the scope and limitations of these drugs wish to take medication to reduce the risk of a further seizure.

Although randomised clinical trials provide useful data for guiding drug treatment, they are of little practical use. The studies are generally short term and usually do not take into account the heterogeneity of patients in terms of epilepsy syndrome, associated comorbidities, and lifestyle factors that direct advice on individual treatment options.[112] This necessity was recognised by the recent NICE guidelines on the management of epilepsy (panel).[2,113]

Antiepileptic drugs should always be introduced cautiously and the dose stepped up gradually. Titration of the drug is usually symptom-led, and if seizures are still taking place, the drug should be titrated up to the maximum tolerated dose. If toxic effects occur at any point, the dose should be reduced. If one first-line drug fails at the maximum tolerated dose, it should be substituted with another such drug. If all first-line drugs fail then second-line options should be added (table 2). Monotherapy is preferable because polytherapy increases the possibilities of poor compliance, drug interactions, teratogenicity, and long-term toxic effects. There are, however, some individuals for whom polytherapy cannot be avoided. Consideration has been given to the notion of rational polytherapy—ie, the use of combinations of drugs with different putative mechanisms of action, aiming at synergy of effect but not of adverse effects.[114] However, apart from some evidence that lamotrigine and sodium valproate might be better in combination that either alone,[115] there is no consistent evidence that synergisms exist between different drugs, and this area needs further investigation.

Despite the existence of many antiepileptic drugs, a third of people who develop epilepsy continue to experience seizures unabated.[26] For most of these individuals, in particular those who are not candidates for curative epilepsy surgery, the only hope for improved seizure control lies with drugs to which they have not been previously exposed. New agents are rapidly being developed and efforts are being directed at disease modification in addition to symptom control.[116]

Adverse drug effects

Occasionally, seizures can be aggravated by antiepileptic drugs.[117–120] Before attributing exacerbation of seizures to a drug, alternative explanations need to be excluded, such as natural fluctuation of seizure occurrence, irregular adherence to the prescription, comorbid illness, and development of tolerance.[120] Most information on aggravation of seizures is based on anecdotal case reports or case series and should be interpreted cautiously. In practice, the possibility of seizure aggravation should be considered—in particular when treating idiopathic generalised epilepsy with drugs that modulate sodium channels and certain GABAergic drugs—and consequently, these drugs are best avoided in the initial management of this disorder (table 2).[120]

The potential clinical implications of the well established adverse effects of older antiepileptic drugs on bone metabolism and density[121–124] have generated studies investigating the extent of these problems and associated risk factors. Whether or not this problem is also associated with the newer drugs is yet to be proven. There have been renewed concerns about the potential teratogenicity of sodium valproate.[125–132] Another issue is that sodium valproate exposure in utero might impair neuropsychological development, even in children without overt physical malformation.[133,134] Prospective studies are being done in both the UK and the USA to address this issue, and are of great importance because sodium valproate is still one of the most effective drugs, especially for some forms of idiopathic generalised epilepsy.[135]

Antiepileptic drugs that interact with hormonal contraceptives usually do so by enhancing clearance of the oestrogen component.[136] This potential for contraceptive failure is an important issue in the treatment of women with epilepsy. A different form of interaction with oral contraceptive steroids has been described: levels of lamotrigine are substantially reduced by the oestrogen component of oral contraceptives,[137] which has clinical implications because initiation of oestrogen contraception could therefore result in recurrence or exacerbation of seizures.

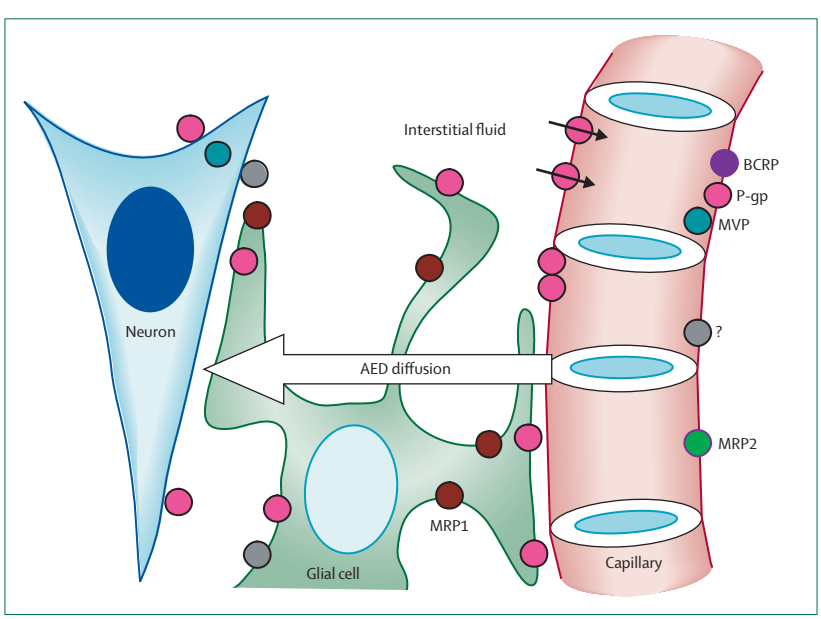

Figure 7: **Schematic illustration of drug transporter hypothesis of antiepileptic drug resistance**
Small circles=multidrug transporters. MRP1, MRP2=multidrug-resistance associated proteins 1 and 2. BCRP=breast cancer resistance protein. MVP=major vault protein.

Pharmacogenetics and drug resistance

Pharmacogenetics addresses the effect of genetic variation on drug response and adverse effects. Environmental factors (eg, alcohol abuse) can partly account for resistance to drugs, but are poorly understood. Major advances in genetic biotechnology make understanding the genetic contribution to varying drug responses a realistic possibility. Little is known of epilepsy pharmacogenetics, apart from the acknowledged effect on phenytoin dosing of variation in the gene encoding the metabolising enzyme CYP2C9, although pretreatment genotyping of such variation has not found a place in clinical practice. Pharmacogenetics holds the promise of therapy that more closely suits an individual's profile and type of epilepsy. Pharmacogenetics will support, and not supplant, the treating physician, who can place the cost-effective interpretation of data in the individual's clinical and environmental context.

Common variation in the gene *SCN1A* affects the maximum dose of phenytoin or carbamazepine, which act on the sodium channel subunit encoded by this gene.[138] Although the recorded genotypic variation explained only around 5% of the dose variation seen, the implementation of dosing pharmacogenetics could lead to more effective use of existing specific antiepileptic drugs in patients who are constitutionally suited to them. However, much more research is needed to make use of data on individual genetic variation, to guide drug choice, and to predict dosing and response.

Pharmacoresistance per se has received fresh attention:[139] two key hypotheses that are not mutually exclusive have emerged for the underlying mechanisms. The target hypothesis postulates alteration in drug targets at some stage, leading to poor response to drug treatment.[140] The transporter theory posits that certain multidrug transporters expressed in the brain could reduce antiepileptic drug concentration around neurons in the seizure focus by active export away from neurons, back into capillary lumina (figure 7). Variation in the gene *ABCB1* encoding one such transporter, P glycoprotein, was shown to associate with a phenotype of broad drug resistance.[141] However, a formal replication did not lend support to the original finding.[142] Replication and functional explanation of reported associations are essential before therapy or prognostication can depend on such reports. However, the potential of pharmacogenetics makes such investment worthwhile, since results generated in this way could lead to improved management

more quickly than through an understanding of disease susceptibility genetics.

Surgery

In view of the rapidly diminishing chances of becoming seizure-free after trying three antiepileptic drugs,[143] individuals continuing to have focal seizures should have surgical treatment considered early on. The most common operations are temporal lobe resections, which are cost-effective procedures[144] carrying a 60–70% chance of making the individual seizure free[145,146] with improved quality of life.[147] The chance of a good outcome is greatest if the underlying cause is removed, driving research efforts to improve imaging detection of the cause before operation. If surgical treatment is proposed, localisation of the site of seizure onset or critical point in a network, is necessary. This localisation is usually accomplished with longlasting scalp video EEG recordings. If the site of seizure onset is not clear, or if there is discrepancy between data, invasive EEG recordings might be necessary, with depth electrodes placed stereotactically within the brain tissue or subdural strips and grids of electrodes placed on the surface of the brain. This technique has restricted spatial sampling, and the approach needs to be individualised for each patient to test specific hypotheses that can be generated with functional imaging.[148]

Complete seizure control might not be a realistic objective, but useful palliation can still be gained with a cerebral resection or techniques such as corpus callosotomy and multiple subpial transection. Vagal nerve stimulation, by a subcutaneous pulse generator, can also provide palliation when resective surgery is not a viable option.[149] On average, a 50% reduction of seizures can be expected in up to 30–40% of patients, but seizure freedom is seldom seen.[150] Deep brain stimulation is being assessed for refractory epilepsy, and at present there is no consensus about its usefulness. With the heterogeneity of structural and functional networks that might sustain epilepsy, the likelihood of achieving more than palliation through an effect on a final common pathway does not seem probable.

New treatment prospects

There remain difficulties in epilepsy treatment. Treatment should be individualised but remains empirical, and antiepileptic drugs fail for some patients. Despite the success of surgery in the treatment of such refractory focal epilepsy, it is suitable for less than 10% of these patients.[151] Thus, new treatment strategies remain necessary.

Early prediction of seizures could have an enormous effect on the treatment of epilepsy, since it would allow action to be taken to prevent the seizure occurring—such an approach is already used in catamenial epilepsy, and by people who have lengthy aura. Use of EEG in predicting seizures is a fast-growing technique. Non-linear analyses of signals can anticipate seizures by several minutes. In practical terms, at present there are limitations of sensitivity and specificity, and the usefulness of this method in clinical practice is yet to be established.[152–154]

With advances in stem-cell science and viral gene expression systems, interest has grown in focal approaches to the treatment of epilepsy.[155] At present, such approaches remain experimental. Focal treatments use two approaches: (1) focal application of drugs, cells, or a virus to the epileptogenic zone; (2) focal application to areas that regulate seizure threshold, propagation, or both. The first approach is dependent on identifying where the seizures originate. The advantage over surgery is that tissue destruction can be avoided, and thus this approach could be used in eloquent cortex. If the focus cannot be identified, similar methods could be used to express or release antiepileptic compounds into areas that regulate cortical excitability and seizure threshold.[156]

Conclusions

The epilepsies are common, and heterogeneous by virtue of different seizure types, syndromes, causes, comorbidities, and other individual patient factors. Although up to 70% of patients will have their condition controlled with drugs, the remainder continue to have seizures and their negative effects on quality of life, morbidity, and risk of mortality. Surgical treatment is life-changing for a small proportion of patients. As genomics and proteomics unfold, the causation of epilepsies will become better understood, and will prompt selection of optimum treatment and development of new treatments. For selected individuals, methods to anticipate seizures and local drug delivery hold promise. Individuals with epilepsy will still need sympathetic, well informed professional advisers to integrate the science with a person's life and thus generate holistic care plans.

Conflict of interest statement

J S Duncan has been consulted by and received fees for lectures from Eisai, GE Healthcare, Pfizer, GlaxoSmithKline, SanofiAventis, and UCB; he has had departmental and grant support from MedTronic, Cyberonics, and VSM MedTech. J W Sander has been consulted by and received research grants and fees for lectures from Eisai, Pfizer, Sanofi-Aventis, UCB, and Schwartz Pharma; he has received fees for lectures from Novartis. S M Sisodiya has received fees for lectures or research grant support from Pfizer, GlaxoSmithKline, and UCB. M C Walker has been consulted by, received fees for lectures and research grants from UCB; he has received fees for lectures from Pfizer, has been consulted by Eisai, and has received research grant funding from Johnson & Johnson.

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