Epilepsy in adults

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Epilepsy is one of the most common serious brain conditions, affecting over 70 million people worldwide. Its incidence has a bimodal distribution with the highest risk in infants and older age groups. Progress in genomic technology is exposing the complex genetic architecture of the common types of epilepsy, and is driving a paradigm shift. Epilepsy is a symptom complex with multiple risk factors and a strong genetic predisposition rather than a condition with a single expression and cause. These advances have resulted in the new classification of epileptic seizures and epilepsies. A detailed clinical history and a reliable eyewitness account of a seizure are the cornerstones of the diagnosis. Ancillary investigations can help to determine cause and prognosis. Advances in brain imaging are helping to identify the structural and functional causes and consequences of the epilepsies. Comorbidities are increasingly recognised as important aetiological and prognostic markers. Antiseizure medication might suppress seizures in up to two-thirds of all individuals but do not alter long-term prognosis. Epilepsy surgery is the most effective way to achieve long-term seizure freedom in selected individuals with drug-resistant focal epilepsy, but it is probably not used enough. With improved understanding of the gradual development of epilepsy, epigenetic determinants, and pharmacogenomics comes the hope for better, disease-modifying, or even curative, pharmacological and non-pharmacological treatment strategies. Other developments are clinical implementation of seizure detection devices and new neuromodulation techniques, including responsive neural stimulation.

Lancet 2019; 393: 689–701

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Published **Online** January 24, 2019 http://dx.doi.org/10.1016/S0140-6736(18)32596-0

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Introduction

Epilepsy, one of the most common brain conditions, affects over 70 million people worldwide. It is characterised by a lasting predisposition to generate spontaneous epileptic seizures and has numerous neurobiological, cognitive, and psychosocial consequences.[1] Nearly 80% of people with epilepsy live in low-income and middle-income countries. In many parts of the world, epilepsy is stigmatised and people might not get treatment. Over 75% of those with active epilepsy are untreated and this constitutes a major treatment gap, mostly concentrated in low-income and middle-income countries.[2] Epilepsy should be a global health priority, especially as cost-effective treatments are available, which can substantially reduce morbidity, disability, and mortality.[3,4] In 1997, WHO in conjunction with the International League Against Epilepsy and the International Bureau for Epilepsy launched the Global Campaign Against Epilepsy, which resulted in the 2015 World Health Assembly urging all states to address the specific needs of people with epilepsy.[5]

Epilepsy is defined as: two unprovoked seizures occurring more than 24 h apart; a single unprovoked seizure if recurrence risk is high (ie, >60% over the next 10 years); or a diagnosis of an epilepsy syndrome.[1] Epilepsy is considered resolved for people who had an age-dependent syndrome but have passed the applicable age and are seizure-free, or in other cases of epilepsy, for those who have been seizure-free for the past 10 years with no medication for the past 5 years.[1] Proper classification schemes are needed to guide the best possible management: what might be the best medication for one syndrome could be deleterious for another. In 2017, the International League Against Epilepsy updated the classification and terminology of seizures[6,7] and epilepsy.[8] The new scheme incorporates progress in the understanding of the epilepsies.

Too often, people are categorised as simply having epilepsy whereas the diagnosis should be as specific and as precise as possible. Classification is made at three levels: seizure type, epilepsy type, and syndrome (figure 1). At each stage, cause and comorbidities should be identified as these might have important therapeutic implications. The causes are divided into six categories: genetic, structural, metabolic, infectious, immune, and unknown.[8] Seizures are first classified by onset as either focal, generalised, or unknown. Level of awareness subdivides focal seizures in those with retained awareness and impaired awareness. Focal seizures are further categorised by the earliest and most prominent motor or non-motor manifestation (figure 2).[6,7] All classifiers are optional and depend on the available level of detail. Generalised seizures are divided into motor and non-motor (absence) seizures. Seizures of unknown onset might have features that can still be classified. A common scenario includes someone presenting with convulsions without clinical evidence for a focal or a generalised onset. These seizures can be classified as unknown onset tonic-clonic seizures. In those presenting with convulsions of presumed focal onset, the term focal to bilateral tonic-clonic is recommended,

Search strategy and selection criteria

We searched PubMed and SCOPUS for publications in English from Jan 1, 2008, to May 1, 2018, with the keywords "epilep*", "antiepileptic drug", "EEG", "MRI", "immunology", "seizure detection", "seizure prediction", "SUDEP", "mortality", "gene*", "surgery", and "mechanisms". We have arbitrarily chosen seminal work, clinical studies with the highest level of evidence, or the highest number of most recent meta-analysis. We have also used some earlier articles and reviews, if particularly pertinent to the discussion.

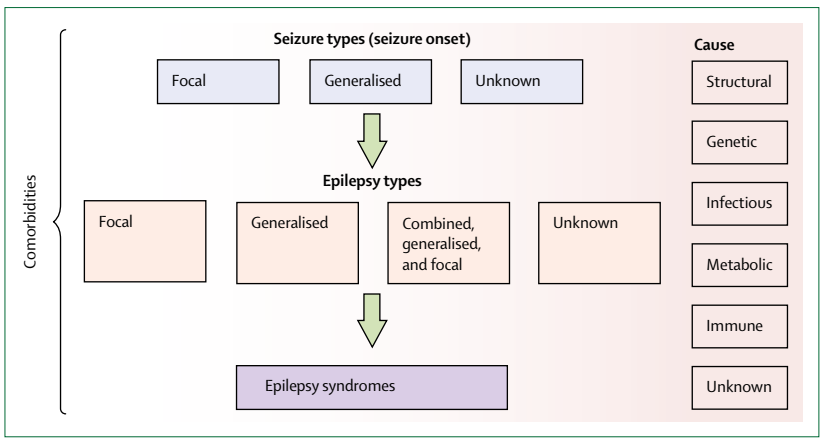

Figure 1: **The International League Against Epilepsy framework for the classification of epilepsies**
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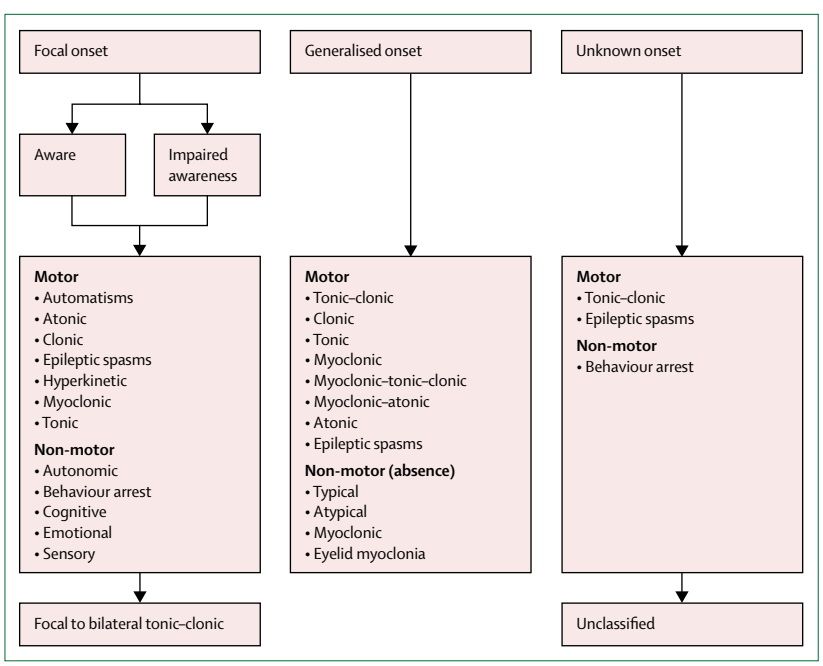

Figure 2: **The International League Against Epilepsy framework for the classification of epileptic seizures**
Reproduced with permission from Wiley, The International League Against Epilepsy.[7]

whereas generalised tonic-clonic seizures are restricted to those with generalised epilepsy. Epilepsy types are divided into four categories: focal, generalised, combined generalised and focal, and unknown. The new category of combined generalised and focal epilepsy is used for those presenting with both seizure types. Common examples are Dravet or Lennox-Gastaut syndrome. The highest level of precision can be obtained by identifying an epilepsy syndrome. This diagnosis results from a cluster of clinical features including age of onset, seizure types, comorbidity, EEG, and imaging features. The International League Against Epilepsy's educational website provides guidance for the diagnostic work-up.

For the **International League Against Epilepsy's educational website** see http://www.epilepsydiagnosis.org

Epidemiology

Epilepsy incidence in high-income countries is consistent across different regions with an incidence around 50 (range 40–70) per 100 000 per year.[9–13] It is bimodally distributed with two peaks: in infants less than 1 year old and in people over the age of 50 years. In people older (>50 years), the incidence goes up with increasing age and the highest incidence is in those over the age of 70 years. For unknown reasons, the incidence is higher in low-income countries than in high-income countries, and usually above 80–100 per 100 000 people per year; however, a substandard health-delivery system, poor hygiene, poor basic sanitation, and a higher risk of infections and traumatic brain injury might contribute.[11,14] Regardless of the geographical location, the prevalence of active epilepsy is usually between four and 12 per 1000.[9–12] Risk factors vary by age group. Brain development malformations are usually present in epilepsy that develops before adulthood. Epilepsy associated with head trauma, infections, and tumours might occur at any age. Cerebrovascular disease is the most common risk factor in older people. Geographical location is important because parasitic conditions such as falciparum malaria, neurocysticercosis, and onchocerciasis are among the most common preventable risk factors for epilepsy worldwide.[17]

In high-income countries, over two-thirds of people with epilepsy achieve long-term remission, usually soon after diagnosis.[15] The overall good prognosis is often attributed to the widespread use of antiseizure medication. Many people in low-income countries enter long-term remission without medication, supporting the suggestion that prognosis in some is independent of drugs.[16] Overall, up to a third of people have drug-resistant epilepsy. The increasing number of available drugs has had only a minor, if any, benefit in terms of improved outcomes, such as people becoming seizure-free.[17] It is possible that the true number of people with drug-resistant epilepsy is overestimated. A problem in all epidemiological studies is pseudo drug resistance, which might result from misdiagnosis, non-adherence, or inappropriate treatments. For some, epilepsy is a dynamic condition alternating between drug-responsive and drug-resistant states and this might alter the numbers depending on which state someone is in at the time of case ascertainment.[15,16,18]

Mortality

Premature mortality in people with epilepsy poses a great public health problem as some deaths are preventable. Comorbidities are the most important cause of death, particularly soon after diagnosis.[19,20] Mortality in low-income countries is in general higher than in high-income countries,[21] but its causes differ. Deaths due to external causes (eg, accidents) seem more prevalent in low-income countries than in high-income countries. Up to a third of all premature deaths are either directly (eg, status epilepticus, injuries, sudden unexpected death

in epilepsy [SUDEP]) or indirectly (eg, aspiration pneumonia, suicide, drowning) attributable to epilepsy.[22]

SUDEP is one of the main causes of epilepsy-related death and has attracted substantial attention.[22] The cause is unknown and there are no effective preventive measures apart from nocturnal supervision.[23] The diagnosis requires an autopsy to rule out an underlying cause of death.[24] SUDEP is mostly unwitnessed and sleep-related.[25] Many individuals with SUDEP are found in prone position[26] with evidence of having had a recent seizure. Rare cases occurring during video-EEG monitoring suggest that SUDEP is preceded by a convulsion followed shortly by apnoea and then asystole.[27] Incidence is 1·2 per 1000 person-years[28,29] with a peak for those aged 20–40 years. The young average age at death explains why SUDEP, despite its low incidence, is the second greatest neurological cause of potential years of life lost.[30] Frequent convulsions are the major risk factor,[28] particularly if nocturnal,[25,31] and nocturnal supervision might be protective.[31,32] Reducing seizure frequency seems to be the best way to reduce SUDEP risk.[28,33] An open discussion about the consequences of epilepsy, including death, is recommended as an essential part of counselling, particularly of those at high risk.[28]

Pathophysiology

Epileptogenesis is the process of converting a non-epileptic brain into one capable of generating spontaneous, recurrent seizures.[34,35] The process is conceptualised to result from an imbalance between excitatory and inhibitory activity within a neuronal network, so that it becomes likely to function in an excessive, hypersynchronous, oscillatory manner, which when sustained, disrupts normal neuronal processing and is capable of disrupting other neuronal networks.[34] For generalised epilepsies, epileptogenic networks are widely distributed, involving thalamocortical structures bilaterally.[7,36] For focal epilepsies, networks involve neuronal circuits in one hemisphere, commonly limbic or neocortical.[7] The imbalance between excitation and inhibition resulting in epileptogenic networks is not necessarily only an increase of excitation or a loss of inhibition; an aberrant increase in inhibition can also be pro-epileptogenic in some circumstances, such as absence seizures[37,38] or limbic epilepsies in the immature brain.[39] Most generalised epilepsies are thought to have a genetic basis.[40] By contrast, focal epilepsies were thought to be mostly underlined by structural cerebral abnormalities, in particular in drug-resistant epilepsy.[41–43] An increasing number of inherited and de-novo genetic mutations have, however, been found in non-lesional focal epilepsy.[44–48]

The pathophysiological mechanisms by which structural abnormalities cause seizure activity are not fully understood. Seizures result primarily from abnormal activity in cortical neurons, although glial cells and axons in the white matter might become secondarily involved.[49] Much of the understanding derives from animal models involving an epileptogenic brain insult, with proconvulsant chemicals, electrical stimulation, or traumatic brain injury.[49,50] The relevance of extrapolating these models to humans has been questioned.[51]

The best ascertained epileptogenic lesion is mesial temporal sclerosis, often found in resected brain tissue from people who had surgery.[52–54] The characteristic pathological findings are loss of excitatory and inhibitory neurons in specific subfields, axonal sprouting and synaptic reorganisation, and alterations in glial function and structure.[52,55–58] An initial brain damage is thought to result in hippocampal cell loss, followed by collateral axonal sprouting and a reorganisation of synaptic circuitry, eventually affecting the balance between inhibition and excitation in limbic circuits until spontaneous seizures ensue. Many different neurobiological processes have been implicated as potential targets for antiepileptogenic or disease-modifying therapies.[59,60] These processes include accumulation of neurodegenerative proteins (such as human tau and β-amyloid), neurogenesis, pro-inflammatory processes (such as interleukin 1β, transforming growth factor β and activin receptor-like kinase), changes in neuronal voltage and ligand gated ion channels, neurotransmitter release or uptake characteristics, and intracellular signalling cascades (such as brain-derived neurotrophic factor and tropomyosin receptor kinase, the mechanistic target of rapamycin [mTOR] pathway, adenosine/adenosine kinase, and microglia activation).[59,60] Many of these processes are thought to be driven by epigenomic changes induced by the epileptogenic insult.[61,62] Which, if any, of these processes are fundamental to epileptogenesis is still to be established and there is no clinically validated antiepileptogenic therapy.

Genetic basis and contribution

More than 30 different mutated genes have been found in families with rare autosomal dominant monogenic epilepsies with high penetrance.[63,64] The initial mutations discovered were primarily in genes coding for ion channels; however, several mutations in non-ion channel genes including genes for neuronal receptors, transcription factors, and enzymes have been found. People with familial monogenic epilepsies represent a small percentage (5–10%) of all genetic epilepsies.[65,66] The underlying causes of the majority of cases of presumed genetic generalised epilepsies, such as juvenile myoclonic epilepsy, are still unknown despite intensive investigations.[64,67,68] The genetic cause of these common epilepsies is likely to be complex, involving contributions from multiple genes, either within individuals or between different individuals with the same syndrome.[65,66]

Traditionally, genetic abnormalities were believed to cause mainly generalised epilepsies, in particular the idiopathic generalised epilepsies and developmental epileptic encephalopathies.[40] Focal epilepsies, however, can also have a genetic basis.[44,45] Mutations associated with focal epilepsies often involve genes in the mTOR pathway, but can involve voltage gated (eg, *SCN1A*)

or ligand gated channels (eg, *GABRG2*).[46–48] Evidence suggests that the presence of a family history of epilepsy increases the risk for the development of focal acquired epilepsy such as those following traumatic head injury.[40,69] There is probably a spectrum in the genetic contribution: from individuals in whom genetics are the primary cause through to those whose underlying genetic background predisposes them to the development of epilepsy after an acquired brain insult—ie, a so-called second hit.

Advances such as genome-wide association studies,[70] whole exome sequencing,[71] and whole genome sequencing are beginning to uncover the genetic architecture of some of these epilepsies.[68] The contribution of common variants versus multiple rare mutations has been long debated,[66] but evidence from a study in 2017 suggests that both are likely to have a role.[68] Most advances have been made in severe developmental and epileptic encephalopathies, in which whole genome sequencing approaches identified genetic mutations in 30–50% of people, with more than 60 genes implicated involving a wide range of cellular proteins including ion channels, synaptic proteins, and transcriptional regulators.[72] Most commonly these genetic abnormalities are caused by de-novo mutations, but recessive or X-linked mutations, mosaicism, and copy number variants also contribute.[72,73]

Comorbidities

Epilepsy rarely stands alone and the presence of comorbidities is the norm: more than 50% of people with epilepsy have one or several additional medical problems. Psychiatric conditions (eg, depression, anxiety disorder, psychosis, and autism spectrum disorder) have long been associated with epilepsy, but more recently somatic conditions (eg, type 1 diabetes, arthritis, digestive tract ulcers, and chronic obstructive pulmonary disease) have also been linked to epilepsy.[74] Several possible associative mechanisms have been identified. Artifactual associations or merely a chance association cannot be ruled out because people with several illnesses are likely to be referred onwards to other specialists, thus leading to a selection bias because those with a comorbid condition are diagnosed earlier than those without a comorbid condition. The associations do, however, not fully explain the mechanisms. A causative relationship (eg, a stroke causing epilepsy) is the most unequivocal mechanism of association. Some conditions can result from epilepsy or its treatment (eg, the effects of antiseizure medications or the consequences of seizures such as fractures). A shared risk factor is an underlying factor or condition that results in the development of two or more distinct conditions. The risk factor can be of environmental, genetic, neurochemical, physiological, or structural origin.[75] Genetic factors can affect the relation between epilepsy and comorbidities in various ways. They can be the basis for developing epilepsy or a comorbidity, or the source of a shared risk factor for epilepsy and a comorbidity (eg, epilepsy, cortical tubers, and cardiac rhabdomyoma in an individual with a *TSC2* mutation).

Comorbidity affects quality of life, results in frequent health-care visits, and higher health-related costs.[76] The prevalence of some comorbidities is up to eight times higher in people with epilepsy than in the general population. These comorbidities include dementia, migraine, depression, anxiety, heart disease, peptic ulcers, and somatic autoimmune diseases. Epilepsy management should include screening of comorbidities because the efficacy and tolerability of antiseizure medications is often affected by comorbid conditions.[75]

Panel 1: Key points in the diagnosis and management of epilepsy (adapted from National Institute for Health and Care Excellence[78])

- Diagnosis should be promptly made by a specialist with an interest in epilepsy (if available)
- The clinical decision as to whether or not an epileptic seizure has occurred should be based on both the description of the events and a review of symptoms.
- Electroencephalogram should only be done to support diagnosis when the clinical history suggests it
- MRI should be used to identify structural abnormalities in people who develop epilepsy, in whom a focal onset is presumed
- Seizure types and epilepsy syndromes, causes, and comorbidities should be determined, because incorrect classification can lead to inappropriate treatment and persistence of seizures
- Initiation of appropriate treatment recommended by a specialist with an interest in epilepsy (if available)
- Treatment should be individualised according to seizure type, epilepsy syndrome, comedication and comorbidity, individual's lifestyle, and personal preferences.
- Individuals with epilepsy and their family, carers, or both should participate in all decisions about their care, considering any specific needs
- Epilepsy diagnosis needs to be critically evaluated if events continue despite an optimal dose of a first-line antiseizure medication
- All adults with epilepsy should have a comprehensive care plan including lifestyle and medical issues
- Comprehensive provision of information about all aspects of the condition
- Regular structured review at least once a year

Diagnosis

Epilepsy is a complex diagnosis without an easy accessible gold standard. A detailed history together with a reliable eyewitness account is the key to diagnosis. The decision as to whether a seizure has occurred or not is based on a combination of symptoms and signs, because no single feature is specific for epilepsy (panel 1).[77,78] Adding to the complexity, epilepsy is polymorphic with many presentations and a myriad of mimics. Non-epileptic paroxysmal events should always be ruled out because misdiagnoses of epilepsy are common and potentially damaging.[79] Transient loss of consciousness is the most common presentation with syncope, and psychogenic or functional causes are the most important epilepsy mimics.[80] An electrocardiogram should be considered in all adults with possible seizures, particularly if presenting with

transient loss of consciousness.[78,81] Home videos of events can be of great diagnostic help, yet require expertise to differentiate epileptic from non-epileptic events.[82–84] An abnormal electroencephalogram (EEG) does not define epilepsy but interictal epileptiform discharges might provide support for a clinical diagnosis.[78] An abnormal EEG is most helpful to determine the likely epilepsy type (focal *vs* generalised), to diagnose an epilepsy syndrome, and to assess recurrence risk.[85,86] Newly developed computerised tools might improve quality of EEG assessment and reporting.[87] In individuals who present diagnostic difficulties after clinical assessment and standard EEG, long-term video-EEG monitoring might provide a definitive diagnosis particularly if the episode frequency is high.[88]

Immunology

The discovery of neuronal antibodies has led to the identification of previously unknown encephalopathies and epilepsies.[89] The prevalence of autoimmune epilepsy is not yet known but it seems to affect a substantial minority of those presenting with focal epilepsy.[90] Encephalitis linked to antibodies targeting glutamic acid decarboxylase (GAD)-65, LGI1, CASPR2, and NMDA receptors seems the most common causes. Antibody testing should be considered if the initial evaluation fails to identify an underlying cause and the person presents with symptoms or signs of limbic encephalitis.[89,90] Diagnostic cues include cognitive decline, personality changes, autonomic seizures, dyskinesia, comorbid autoimmune conditions, and mesial temporal changes on MRI (which might evolve into mesial temporal sclerosis).[89–95] Some features might be suggestive for a specific cause, such as faciobrachial dystonic seizures as an early sign of LGI1 encephalitis.[91,96,97] The course of autoimmune epilepsy is mostly subacute but might be insidious. Swift recognition is important as early immunotherapy in NMDA and LGI1 encephalitis seems more efficacious than antiseizure treatment and improves cognitive outcome.[94,97] Anti-GAD65 encephalitis is the exception to the rule as it seems poorly responsive to immunotherapy.[90,95] Serological testing is increasingly valuable but additional cerebrospinal fluid analysis should always be considered, especially when NMDA encephalitis is suspected.[98] Some results should be interpreted with caution, including VGKC positivity in the absence of LGI1 and CASPR antibodies[99] or low GAD65 titres.[90] In those with a definite autoimmune cause, neoplastic screening is recommended, although the yield is generally low except for NMDA.

Imaging

MRI is the standard imaging tool, showing epileptogenic lesions in about 20% of people with newly diagnosed epilepsy and more than half of people with drug-resistant focal epilepsy.[43,100,101] Compared with those without an MRI lesion, people in whom an MRI lesion is detected have a higher risk for recurrence after a first seizure[102] or to continue to have seizures after treatment.[103] MRI must be done with an epilepsy-appropriate protocol comprising at least 1 mm three-dimensional volumetric T1-weighted imaging, axial and coronal T2-weighted, and fluid attenuated inversion recovery sequences (including hippocampal angulation) and axial hemosiderin or calcification-sensitive T2-sequences or susceptibility-weighted sequences.[104] Expert evaluation is probably equally important as some subtle lesions such as hippocampal sclerosis or focal cortical dysplasia can otherwise be missed.[105] In people with drug-resistant focal epilepsy with previous seemingly normal MRIs, rescanning with a different scanner or sequences is often worthwhile (figure 3).

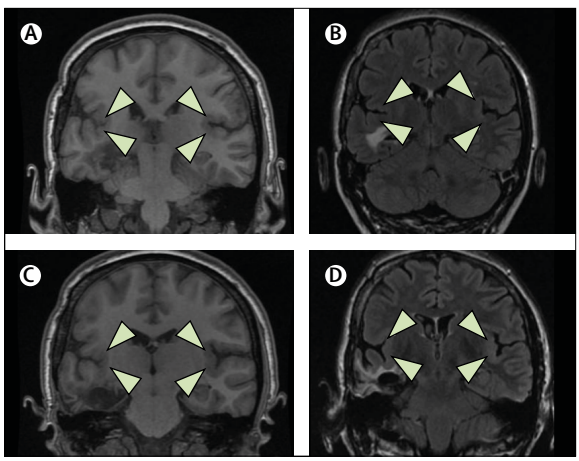

Figure 3: **Epilepsy protocol MRI on a 45-year-old woman who had had two failed right temporal resective surgeries in the 1990s**
A and C are coronal T1-weighted MP-RAGE, and B and D are coronal fluid attenuated inversion recovery sequences acquired on a 3T MRI. Several preoperative and postoperative scans on 1·5T MR scanners had been aquired over two decades, which had been reported to show no epileptogenic lesions. As part of a re-evaluation in 2017 for consideration of further epilepsy surgery, a repeat epilepsy protocol MRI on a 3T scanner showed bilateral perisylvian polymicrogyria (arrowed), which is highly likely to be the cause of the epilepsy.

Treatment

Drug treatment

For most people with epilepsy, antiseizure medications are the main treatment modality, with the aim of stopping seizures at the earliest opportunity without causing side-effects, which can affect quality of life. Seizure remission is also likely to reduce morbidity and to decrease the risk of premature mortality associated with continuing seizures, particularly convulsions.[12,22] Despite the availability of over 25 medications worldwide, the current drugs are effective in only about 66% of individuals in high-income countries,[106] although data suggest that up to 80% could potentially be seizure free.[12] In reality, fewer people are likely to be seizure free. Surveys from 2013 and 2015 in the USA showed that more than half of those taking epilepsy medication were still having seizures.[107] Individuals who are unemployed,

***Panel 2:* List of antiseizure medications by efficacy**

All medications are listed in alphabetical order. The choice of antiseizure medication should take into account the seizure type, epilepsy syndrome, comorbidities, tolerability risks, and individual characteristics. For information on indications, dosage, and side-effects consult the latest national guidelines and information provided by the licence holder (adapted from National Institute for Health and Care Excellence[78] and Moshé et al[110]).

Focal and most generalised seizures
Benzodiazepines, lamotrigine*, levetiracetam, perampanel, phenobarbital, topiramate, sodium valproate, zonisamide

Focal seizures only
Brivaracetam†, carbamazepine, eslicarbazepine acetate, gabapentin, lacosamide†, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin‡

Absence seizures only
Ethosuximide§

Special encephalopathies only
Cannabidiol¶, everolimus||, felbamate**, rufinamide**, stiripentol††

*Might aggravate myoclonic seizures. †Effects on generalised seizures yet unknown. ‡Also effective in infantile spasms. §Also effective in myoclonic seizures. ¶Only in the context of Lennox-Gastaut spectrum and Dravet syndrome. ||Only in the context of tuberous sclerosis complex. **Only in the context of Lennox-Gastaut spectrum. ††Only in the context of Dravet syndrome.

who live alone, or are in low-income households are at higher risk of active seizures.

Despite the large number of available drugs worldwide, only a few are considered first line. Mechanisms of drug action are outside the scope of this review and are reported elsewhere.[108,109] Many drugs can be used for focal and generalised seizures. Others are specific for particular forms of epilepsy—for example, sodium channel modulators are mainly appropriate for focal epilepsies (panel 2). For those who might require treatment, an individualised management plan needs to be put in place promptly. Medication choice is influenced by individual circumstances such as age, sex, child-bearing potential, comorbidities, and tolerability issues in one hand, and seizure type and epileptic syndrome in the other hand (figure 4).[78,110] In older people, who often are taking many concomitant drugs for comorbidities, medications with potential drug-to-drug interactions should be avoided where possible. An example of a positive association would be the choice of an antiseizure medication with antimigraine potential in someone with a history of migraine. The individualised management plan should also incorporate strategies to prevent status epilepticus in those with repeated or prolonged convulsions. Various non-injectable medications can be used at home to terminate prolonged seizures or clusters. Buccal or intranasal midazolam appears to be safe and effective alternative to rectal diazepam.[111,112]

An important question is at what stage, or after how many seizures, should treatment be started because starting treatment after a first seizure will not alter prognosis (figure 4).[78,110] It is good practice to wait for a recurrence before starting treatment. Individuals who seem to have a higher risk of recurrence because of the presence of a structural abnormality, an abnormal EEG, or a pre-existing neurological deficit, however, should start treatment as soon as possible. This approach might also be considered for those who wish to minimise the risk of re-occurring seizures because of personal circumstances (eg, need to operate a vehicle, work requirements, etc), and who fully understand the scope and limitations of the treatment and the risks of recurrence. An exemption to consider is when an individual has very infrequent seizures; this usually requires an informed decision about the gap between seizures, limitations of drug treatment, and risk of recurrence on and off treatment.

Antiseizure medication should ideally be introduced slowly and doses increased in steps depending on symptoms. The drug should be titrated upwards to the maximum tolerated dose if seizures still continue to occur. If tolerability issues appear at any point, a dose reduction is required. If the individual derives no benefit at the maximum tolerated dose, an alternative first-line drug should be initiated. If all first-line drugs fail, then second-line options should be added. In people with frequent and high-risk seizures, additional medication could be considered at an earlier stage. It is better to make only one drug change at a time because it is then possible to determine causality if there is any improvement or deterioration.

Monotherapy is usually the best option as polytherapy might increase the risk of poor adherence, drug interactions, and long-term toxicity. There is also variable evidence of synergetic interactions between drugs regardless of the mechanism of action. Drugs should be discontinued if there is no effect on seizure control or if they are suspected of giving rise to tolerability issues. Drug withdrawal should also be considered in those who achieve long-term seizure freedom when taking antiseizure drugs; nomograms have been developed to predict reliably the recurrence risk and the chance of long-term seizure freedom.[113]

Drug-resistant epilepsy is assumed after the "failure of adequate trials of two tolerated, appropriately chosen and used antiseizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[114] In those cases, it is good practice to rule out all possibilities for treatment failure and to ensure that the diagnosis is correct. Seizure control might require new investigations, or referral to a specialised centre. If the diagnosis is confirmed, alternative non-pharmacological treatments including surgery and neurostimulatory

interventions should be considered. Dietary treatments (eg, ketogenic diet) could improve seizure control in some individuals. Dosing should depend on whether or not the person continues to have seizures or dose-related side-effects or both. Drug levels are not needed to determine the required dosage, but only for a specific purpose—eg, when non-compliance or drug–drug interactions are suspected or to adjust dosing because of hormonal effects (eg, oral contraceptives and pregnancy) on certain antiseizure medications.

Treatment with antiseizure medications is frequently associated with side-effects.[115,116] Neuropsychiatric symptoms (eg, fatigue, dizziness, unsteadiness, and irritability) are the most frequent side-effects, but the medication can affect every organ system. Side-effects are often insidious and might go unrecognised. It is good practice to maintain a high level of vigilance for adverse effects. In women of childbearing potential the risk of teratogenicity should always be taken into account and weighed against all available alternatives.[117] Where possible, sodium valproate should be avoided in view of the high risk of malformations and developmental problems of the exposed child.[118] Counselling should be given to explain the possibility of drug interaction with oral contraceptives. Specific antiseizure medications might induce contraceptive failure, whereas oral contraceptives might also reduce drug levels, particularly of the antiepileptic drug lamotrigine, leading to recurrence of seizures. Antiseizure medications with enzyme-inducing properties might not only reduce efficacy of co-administered drugs such as oral anticoagulants, but also induce deficiencies (eg, folate deficiency), endocrine, metabolic disturbances, or affect bone health.[119,120] Screening for human leucocyte antigen should be considered before initiation of carbamazepine in people of Asian descent, because life-threatening cutaneous adverse reactions are strongly associated with the *HLA-B*15:02* allele.[78] Screening for comorbidity might help to prevent side-effects—for example, avoiding drugs that might promote depression in someone with a mood disorder.

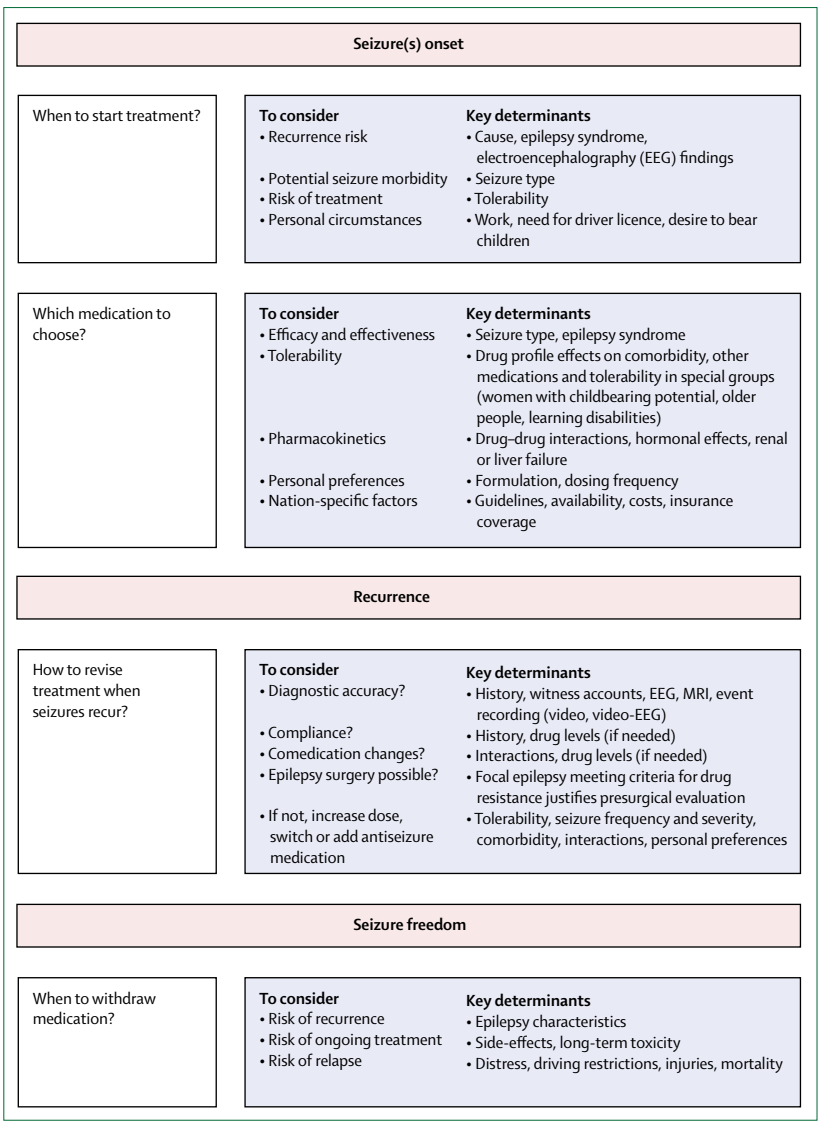

Figure 4: **Key decisions in the pharmacological treatment of epilepsy**
Adapted from National Institute for Health and Care Excellence,[78] Perucca et al,[109] and Moshe et al.[110]

Surgery

People with drug-resistant focal epilepsy might benefit from removal or disconnection of a circumscribed brain region to achieve full seizure-control, or at least stop disabling seizures. The proportion of individuals that are seizure free after surgery ranges from 50–80% in well selected groups.[121] Surgery seems cost-effective and better than the best medical treatment in terms of seizure control and quality of life.[122–125] Benefits of successful surgery also include reduced risk of injury or premature death, opportunity to drive, greater independence, and perhaps improved vocational options. Surgical treatment is, however, still underused and potential candidates are often not referred or are referred late, possibly because of misconceptions and fears (eg, ambiguous view on pharmacoresistance, ignorance of surgical options, negative views on chances of achieving seizure freedom, fear of risks, and of surgery-related personality changes).[126–129] Few resources or little expertise is also a barrier in less wealthy countries, and might be counteracted by raising public awareness and the establishment of regional epilepsy centres.[130]

The selection of appropriate candidates requires comprehensive evaluation to define the epileptogenic zone, estimate risks of postsurgical deficits, and predict outcomes.[131,132] A specialised structural MRI can help to identify the underlying cause and to localise the epileptogenic zone. Examinations of interictal brain function can identify affected regions pointing towards the putative epileptogenic zone and contribute to the prediction of postsurgical deficits. These examinations

include neuropsychological testing, functional MRI (fMRI), ^{18}F-fluorodeoxyglucose (^{18}F-FDG) imaging, tractography, magnetoencephalography, and a combination of fMRI and EEG.[131,133] fMRI, based on blood-oxygen level dependent contrast imaging signal approaches, is increasingly being used to localise or lateralise language and other eloquent cortex, and has mainly replaced the traditional intracarotid sodium amobarbital Wada test.[134] fMRI or Wada tests, along with neuropsychological examinations, can help to lateralise memory function in mesial temporal lobe epilepsy. In other forms of epilepsy, the use of fMRI for memory lateralisation is unclear.[135] ^{18}F-FDG scans done in the interictal period might show hypometabolism in the epileptogenic area and can be helpful if MRI does not show a clear-cut epileptogenic lesion, and can also be predictive of outcome.[136–140] The detection of unilateral temporal hypometabolism in an individual with focal epilepsy has been shown to be independently predictive of a good surgical outcome.[138–141] Magnetoencephalography has been reported to be sensitive and specific in the localisation of the epileptogenic focus in people with focal epilepsy, including those with a normal MRI.[142–144] The scarce availability and expense of magnetoencephalography has, however, restricted its widespread use. Ictal brain dysfunction is evaluated by video-EEG recordings, which help to identify the seizure-onset zone through analysis of seizure semiology and ictal EEG patterns. Single Positron Emission Computed Tomography is done in selected cases and involves intravenous injection of a radiotracer, allowing imaging of cerebral blood flow patterns during, following, or between seizures.[136,145] Co-registration with an MRI scan provides anatomical localisation of the regional perfusion change.[146–148] In up to a quarter of presurgical candidates, additional invasive video-EEG recordings with intracranial depths, strip, or grid electrodes are required if MRI lesions and findings of non-invasive video-EEG recordings are discordant, MRI does not show a clear epileptogenic lesion, or the seizure-onset zone might overlap with eloquent brain regions (eg, motor cortex).[131,149–151] Neuropathological examination after resective surgery helps to characterise the underlying cause and might refine the prognosis of long-term seizure outcome.[152]

The effectiveness of surgery in terms of seizure freedom depends on the underlying pathology, the epileptogenic zone location, the accurate delineation of the zone, and the performance of the neurosurgical intervention.[121] Risks and complications include those inherent to neurosurgical interventions (ie, unintended brain damage because of haemorrhage or infections) and calculated risks related to the specific brain tissue removal (eg, memory deficits because of partial temporal lobe resection). People with an MRI lesion away from eloquent areas, and clinical symptoms and an ictal EEG-pattern consistent with this lesion, have the best chances of becoming seizure free without substantial postsurgical deficits. Individual chances of postsurgical seizure-freedom can be estimated with nomograms.[153] The prototype candidate is a person with temporal lobe epilepsy because of unilateral hippocampal sclerosis.[151] Long-term seizure freedom rates 8–10 years after surgery are around 50–60%,[154,155] with no major differences between those who underwent anterior temporal lobectomy or a selective amygdalohippocampectomy.[156] Reasons for seizure recurrence after surgery are manifold and include false localisation or incomplete removal of the epileptogenic zone, presence of additional distant seizure generators, or progression of the underlying disease.[157] A second operation after thorough re-evaluation leads to sustained seizure freedom in some.[157,158] Palliative surgery with the primary goal to reduce severity or frequency of seizures might be done in some—by callosotomy or removal of leading seizure generator to reduce disabling seizures with recurrent falls.

Neuromodulation

Neurostimulatory techniques are palliative options when surgery is not possible or if surgery failed. The efficacy of neurostimulatory devices has been shown in randomised controlled trials, but the actual benefits might be overestimated because of inherent study limitations and methodical weaknesses.[159] Electrical pulses are applied to peripheral nerves or specific brain areas in response to enhanced rhythmicity to counteract potential seizure generation or propagation. The stimulatory pulses can be delivered in a scheduled manner (open-loop) or in response to seizures (closed-loop). Scheduled stimulation of the vagus nerve reduces seizure frequency by 50% or more in about a third of the patients,[159,160] improves quality of life,[161] and might decrease SUDEP risk.[162] Advanced technology allows application of additional pulses triggered by seizure-related increases of heart rate, which might alleviate seizure severity.[163,164] Deep brain stimulation of the thalamus reduces seizures by more than 50% in about half of the patients and might decrease SUDEP risk.[165] A new approach is to deliver electrical pulses directly to a seizure focus in response to enhanced rhythmicity, changes in frequency, or amplitude of the EEG signals related to seizure generation (responsive neurostimulation, RNS) by implanted intracranial electrodes placed according to the results of preceding invasive presurgical evaluation. This treatment improves seizure control by more than 50% in about half of the patients and might decrease SUDEP risk.[166,167] Antiseizure efficacy seems to increase over time in all neurostimulatory techniques, but this has not been properly assessed.

New diagnostic and treatment prospects

An interesting prospect is the rapid development of wearable, non-EEG based, seizure detection devices, which might alert carers to seizures that could otherwise go unnoticed. Reliable seizure detection could also improve detection of nocturnal seizures which might go

unrecognised, thus resulting in under-reporting.[168–170] Automatic detection, especially of convulsions, seems feasible although detection of other seizure types is still unreliable.[168,171] These devices could help timely interventions, such as repositioning or administration of emergency medication, to prevent SUDEP or status epilepticus. Most devices have been validated in a clinical setting with short-term follow-up. Long-term, home-based trials are needed to explore added value.

Epilepsy surgery with craniotomy might be associated with variable damage of surrounding brain tissue, possibly worsening postsurgical neurological and neuropsychological outcome.[172] Less invasive techniques with a circumscribed abolition of the epileptogenic zone could reduce risks. Stereotactic radiosurgery, radiofrequency thermocoagulation, and laser interstitial thermal therapy damage the target tissue by focally applied irradiation or heat, and have been shown to lead to a favourable seizure outcome in 50–60% of people with drug-resistant focal epilepsy.[173–175] In a prospective trial, however, the proportion of seizure-free people was higher after anterior temporal lobectomy than stereotactic radiosurgery.[176] Laser interstitial thermal therapy might be an alternative to open surgery or radiosurgery, because it has prompt effects on seizure control (as compared with radiosurgery), and the number of seizure-free individuals is comparable to those of resective epilepsy surgery.[177] The antiseizure efficacy and safety of MR-guided ultrasound is currently under investigation.[178]

Few people are suitable for surgical therapies, thus novel epilepsy treatments are an unmet need. The gut microbiome could be a promising target to improve the efficacy of the ketogenic diet.[179] Cannabis products have attracted media attention as a new epilepsy treatment and are often requested in the clinic. Adjuvant use of pharmaceutical-grade cannabidiol has shown some efficacy for people with Dravet and Lennox-Gastaut syndrome.[180–182] Evidence supporting the use of cannabidiol in other refractory epilepsy syndromes is yet still scarce.[183] Fenfluramine hydrochloride might also be efficacious in Dravet and Lennox-Gastaut syndrome.[184,185] In individuals with tuberous sclerosis complex, the model disease of a deregulated mTOR pathway, the mTOR inhibitor everolimus seemed to have a similar but slightly delayed antiseizure efficacy compared with antiseizure medication, suggesting that disease-modifying drugs might improve seizure control.[186] Gene therapy for epilepsy is still experimental. Basic research focuses on molecules interfering with expression of endogenous neuropeptides and microRNA activity, or optogenetic tools to modulate the activity of specific neuronal population by local light application, with the ultimate goal of preventing or interrupting seizures.[187–189]

Conclusion

Epilepsy is a symptom-complex disease with multiple risk factors and in many cases has a strong genetic predisposition, rather than a condition with a single expression and a single cause. Advances in genomic technology are beginning to show the complex genetic architecture of the epilepsies. Comorbidities are increasingly recognised as important aetiological and prognostic markers. Antiseizure medications suppress seizures in up to two-thirds, if not more, of all individuals but do not alter long-term prognosis. Epilepsy is a major burden in terms of quality of life, morbidity, and risk of premature mortality, especially in those who continue to have seizures. Epilepsy surgery is the most effective way to achieve long-term seizure freedom, but is an option only in few people with drug-resistant epilepsy. With improved understanding of epileptogenesis, epigenetic determinants, and pharmacogenomics comes the hope for better, disease-modifying, and curative pharmacological and non-pharmacological treatments.

Contributors

All authors planned the manuscript, did the literature search, contributed to the figures, and wrote, edited, and approved the manuscript.

Declaration of interests

RDT has received research grants from Medtronic and fees for lectures from Medtronic, UCB Pharma, and GlaxoSmithKline. RS has received fees as speaker or consultant from Bial, Cyberonics, Desitin, Eisai, LivaNova, Novartis, and UCB. TJO'B has been consulted by and received research grants and fees for lectures and advisory boards from Eisai, UCB, and Sanofi. JWS has been consulted by and received research grants and fees for lectures from Eisai, UCB, Bial, and Janssen Cilag.

Acknowledgments

RDT receives research support from the Dutch National Epilepsy Fund (15–10), Nuts Ohra Fund, AC Thomson Foundation, The Netherlands Organisation for Health Research and Development, and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, The Netherlands. RS receives research support from the Federal Ministry of Education and Research and the Boll Foundation (Kerpen, Germany). TJO'B receives research support from the National Health and Medical Research Council, National Institute of Neurological Disorders and Stroke, Monash University, and The Royal Melbourne Hospital Neuroscience Foundation. JWS is based at National Institute for Health Research University College London Hospitals Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's Research Centres funding scheme. He receives research support from the Marvin Weil Epilepsy Research Fund, the UK Epilepsy Society, and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, The Netherlands. This work did not receive any specific grant from funding agencies in the public, commercial, or charitable sectors.

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