Adult epilepsy

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Epilepsy is a common medical condition that affects people of all ages, races, social classes, and geographical regions. Diagnosis of epilepsy remains clinical, and ancillary investigations (electroencephalography, imaging, etc) are of aid to determine the type, cause, and prognosis. Antiseizure medications represent the mainstay of epilepsy treatment: they aim to suppress seizures without adverse events, but they do not affect the underlying predisposition to generate seizures. Currently available antiseizure medications are effective in around two-thirds of patients with epilepsy. Neurosurgical resection is an effective strategy to reach seizure control in selected individuals with drug-resistant focal epilepsy. Non-pharmacological treatments such as palliative surgery (eg, corpus callosotomy), neuromodulation techniques (eg, vagus nerve stimulation), and dietary interventions represent therapeutic options for patients with drug-resistant epilepsy who are not suitable for resective brain surgery.

Introduction

Epilepsy is a common chronic brain disorder that affects people of all ages and has no geographical, social, or racial boundaries. Conceptually, epilepsy is a disease of the brain that is characterised by a long lasting predisposition to recurrently generate epileptic seizures.[1,2] An epileptic seizure is defined as a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain".[2] This presentation differs from acute symptomatic seizures, which occur in close temporal relationship with an acute brain insult.[3] In acute symptomatic seizures, a CNS insult (eg, toxins) transiently lowers the seizure threshold; therefore, seizures are not expected to recur once the precipitating factor or condition has been removed or reversed.[3] Epilepsy has neurobiological, cognitive, psychological, and social consequences. Premature mortality remains a major problem in patients with epilepsy globally. This chronic neurological condition poses a substantial burden for health systems, individuals, and their families.[4–7] Therefore, it is important for all health-care professionals to be familiar with this condition. In this Seminar, we have provided the most up-to-date information on classification, epidemiology, pathophysiology, diagnosis, treatment, and lifestyle considerations for patients with epilepsy. We discuss what epilepsy is and whom it affects, why it is important, novel achievements in the research and clinical fields, and what developments are yet to come.

Search strategy and selection criteria

We searched PubMed for articles from Jan 1, 2018 to Dec 31, 2022, with the search terms "epilepsy", "EEG", "MRI", "seizure", "epidemiology", "mortality", "antiepileptic drug", "antiseizure", "surgery", "mechanisms", "autoimmune", "complementary and alternative medicine", "exercise", "sleep", and "diet". Articles written in English were included. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

Classification of epilepsies

As epilepsy is not a single disease entity the diagnosis should be as specific as possible.[8] The International League Against Epilepsy (ILAE) has provided a classification system at three different levels: seizure type (classified into focal onset, generalised onset, or unknown onset), epilepsy type (classified as generalised epilepsy, focal epilepsy, combined generalised and focal epilepsy, or unknown), and epilepsy syndrome (figure 1).[9]

An epilepsy syndrome refers to a collection of specific clinical characteristics that can include seizure types, electroencephalogram (EEG) findings, brain imaging results, and other features (eg, age at seizure onset, comorbidities, seizure triggers, aetiology, and prognosis), which often occur together.[9] It is ideal to make a syndromic diagnosis in a patient who has epileptic seizures (eg, juvenile myoclonic epilepsy, focal epilepsy syndromes with genetic, structural, or genetic-structural aetiologies [eg, sleep-related hypermotor epilepsy, mesial temporal lobe epilepsy with hippocampal sclerosis], etc). Recently, the ILAE has provided detailed classification systems for various epilepsy syndromes.[10,11] However, the epilepsy type could be the final level of diagnosis that is achievable; the clinician might not have sufficient information to make a syndromic diagnosis.[9] Under normal circumstances, and when the resources to collect enough information to make a syndromic diagnosis (such as EEG, MRI) are available, if a clinician is not able to make a syndromic diagnosis of the condition they should at least be able to classify the epilepsy type (panel 1). The diagnostic level establishes the foundation for the treating health-care provider to contemplate an appropriate management strategy for the condition.[12] In some instances of resource-limited settings, classification according to seizure type might be the only reachable diagnosis due to an inability to access EEG or imaging studies, as these diagnostic measures might be necessary to differentiate focal from generalised epilepsy types.[9] In such circumstances, a detailed clinical history of

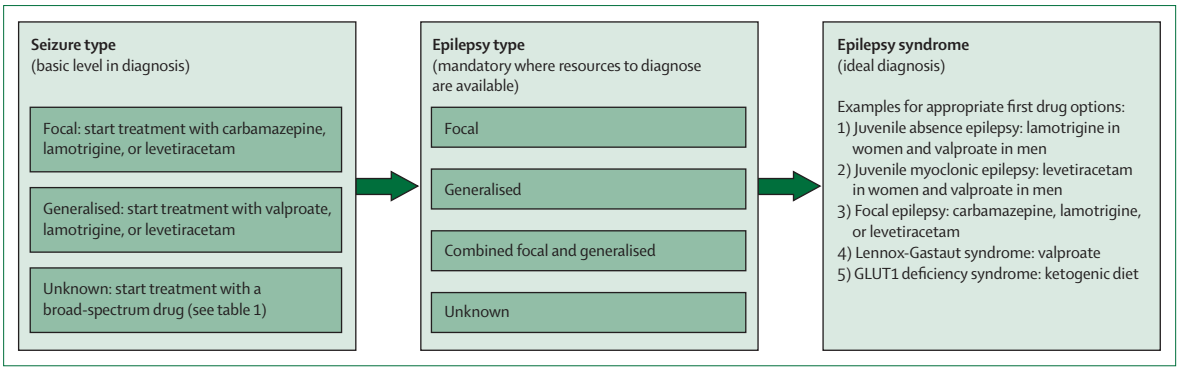

Figure 1: **Framework for classification of seizures and epilepsies and its practical implications**
The suggested treatment options could differ considering other variables (eg, sex, age, comedications, comorbidities, availability, cost).

Panel 1: Key points in the diagnosis of epilepsy type in adult patients with epilepsy

Generalised epilepsy
- Age at seizure onset: usually in childhood, adolescence, or young adulthood (<25 years)
- Aura: not common; if present, is often non-specific (eg, dizziness)
- Ictal events: absence, myoclonic, tonic-clonic, and rarely atonic and tonic seizures
- Postictal state: common after generalised tonic-clonic seizures (not present after absence and myoclonic seizures)
- Family history: might be positive for epilepsy
- Epilepsy risk factors (traumatic brain injury, CNS infections, etc): absent
- EEG: might show generalised spike-waves or polyspikes
- MRI: MRI is not needed if a syndromic diagnosis of an idiopathic generalised epilepsy (based on history and EEG) is made; if performed, it is normal or might show incidental findings (not related to epilepsy)

Focal epilepsy
- Age at seizure onset: at any age
- Aura: common, might be location specific (eg, focal sensory aura)
- Ictal events: focal aware seizures (motor or non-motor), focal impaired awareness seizures (motor or non-motor), and focal to bilateral tonic-clonic seizures
- Postictal state: common after all seizure types (except focal aware seizures)
- Family history: rarely positive for epilepsy (might be positive in familial cases)
- Epilepsy risk factors (traumatic brain injury, CNS infections, etc): might be present
- EEG: might show focal epileptiform discharges
- MRI: might show structural brain abnormality (dedicated epilepsy protocol)

Combined generalised and focal epilepsy
- Age at seizure onset: often in childhood
- Has different seizure types with features from both categories. For example, some patients with Lennox-Gastaut syndrome might have tonic seizures, myoclonic seizures, tonic-clonic seizures, and focal impaired awareness seizures.

Unknown
- Age at seizure onset: at any age
- Aura: none or non-specific (eg, dizziness)
- Ictal events: tonic-clonic seizures
- Postictal state: non-specific (eg, sleepiness, fatigue, confusion)
- EEG: normal
- MRI: normal

the patient is often revealing. If a patient presents with tonic-clonic convulsions without enough clinical evidence to ascertain either a focal or a generalised onset, their seizures can be classified as unknown onset tonic-clonic seizures.[9]

Epidemiology

In a systematic review and meta-analysis of international studies, the point prevalence of active epilepsy was 6·4 per 1000 individuals (95% CI 5·6–7·3) and its incidence was 61·4 per 100 000 person-years (50·8–74·4).[13] A previous systematic review found the median crude incidence rate of cerebrovascular disease to be 149·5 cases per 100 000 people.[14] The prevalence and incidence rates of epilepsy are higher in low-income and middle-income countries compared with those in high-income nations.[13] We estimate the point prevalence of active epilepsy in the world (as of Feb 24, 2023) to be about 51 million people.[15] Similarly, our estimates suggest that every year about 4·9 million people in the world develop new-onset epilepsy, based on the world population and the incidence rate of epilepsy. High-quality studies on the epidemiology of epilepsy types or syndromes are scarce, but it seems that about two-thirds of all epilepsies are focal onset in nature, about a-fifth of all epilepsies are idiopathic generalised epilepsies, and the rest are other epilepsy

types.[16,17] Despite the global nature of the prevalence of epilepsy, there is a considerable epilepsy treatment gap defined as the proportion of people living with active epilepsy who do not receive appropriate treatment of the total number of people living with active epilepsy in a population.[18] Common risk factors and causes of epilepsy vary by age group. Cerebrovascular and neurodegenerative diseases are common risk factors in older people, whereas epilepsy associated with traumatic brain injury, infections, and tumours might occur at any age. Geographical location is also an important factor. For example, parasitic conditions such as malaria (in sub-Saharan Africa) and neurocysticercosis (in Asia, sub-Saharan Africa, and Latin America) are among the most common preventable aetiologies of epilepsy in some low-income and middle-income countries, whereas traumatic brain injuries are particularly common in war-torn regions and nations in the world.[8,19] Although patients with epilepsy are subject to similar causes of death as those without epilepsy, mortality in patients with epilepsy is greater than that in the general population. Sudden unexpected death in epilepsy (SUDEP), status epilepticus, drowning, injuries, and directly related causes (eg, brain tumour) are epilepsy-related threats.[4,20] The standardised mortality rate of patients with epilepsy in low-income and middle-income countries (3·7) is higher than that in high-income countries (2·3); the reason for this higher mortality rate is not known, but could be due to methodological differences across studies.[21] The incidence rate of SUDEP is 23 times the incidence rate of sudden death in the age-matched general population.[22] For SUDEP, young adulthood and the presence of tonic-clonic seizures appear to be the most consistent risk factors in published studies. Other important risk factors include nocturnal seizures, sleep (particularly in the prone position), high seizure frequency, intellectual disability, inadequate treatment, and male sex.[4]

Pathophysiology

Focal epilepsy can be defined by a seizure onset localised to one or multiple circumscript brain regions as indicated by seizure semiology or neurophysiological recordings. A generalised epileptic seizure occurs due to hyper-synchronised electrophysiological bursts simultaneously in both hemispheres. Pathophysiological concepts in epileptology have changed considerably over the past decades.[8,23] The primarily neurophysiology-driven cellular approach argued for an imbalance between excitation versus inhibition through aberrantly assembled ion channels or neurotransmitter receptor subunits as a fundamental basis. This hypothesis has been reproduced in animal models, but seems oversimplified based on advancements in the understanding of epilepsy. Technical advancements in human intracerebral recordings then evolved into concepts of larger, aberrantly oscillating cortical networks that might also engage subcortical regions.[24] This notion facilitated the contemporary recognition of neurostimulation techniques in the current treatment portfolio for drug-resistant epilepsy. Modern multiomics approaches have identified, however, an increasing number of candidate genes for epilepsy across many epilepsy syndromes. Published studies highlighted genetic alterations in ion channels and synaptic transmission (including *SCN1A* and *GRIN1* genes, and many more) in generalised epilepsies.[25,26] These alterations differ from structural focal epilepsies in which, for example, mosaic alterations of the mammalin target of rapamycin (mTOR) or mitogen-activated protein kinase signal transduction represent pathogenic key events.[27] Single-cell genomics further exposed the susbtantial burden of brain somatic gene variants in our trillions of neurons evolving from the approximately 30 mitotic cycles of neuronal divisions to build the human neocortex.[28] Each patient's individual brain mosaicism is likely to contribute to or modify the seizure threshold and also change with age.[29]

Any change to the human neocortex with its excitable neuronal network structure can cause seizures and eventually progress into a hyperexcitable epileptogenic disease condition. This knowledge reflects well on the recognised spectrum of focal brain lesions associated with focal epilepsies. In the temporal lobe, the site of the most common epilepsies in adults, epileptiform activity eventually imprints the epigenetic coding machinery of neurons in support of epileptogenesis—an epilepsy diary in support of epigenetic memory by DNA methylation.[28] Whether this holds true also for neocortical epileptogenesis remains yet to be shown.[30] Indeed, surgically amenable focal epilepsy encompasses a well-recognised spectrum of structural lesions that are histopathologically detectable in human brain samples. The most common lesions in patients amenable to epilepsy surgery include hippocampal sclerosis, low-grade developmental brain tumours, and malformations of cortical development (eg, focal cortical dysplasia).[31] However, not all of these lesions can always be considered amenable to surgical resection.

Diagnosis

Epilepsy is a clinical diagnosis. Unless one happens to witness a seizure, the diagnosis of epilepsy relies on the discernment of the physician on the basis of the history provided by the patient and their caregivers. When evaluating a patient with a seizure, the physician should determine whether an epileptic seizure has occurred or whether a condition exists that mimics epilepsy (eg, syncope, functional (psychogenic) seizures, panic attacks, sleep disorders, and movement disorders). Signs and symptoms that precede the attack or occur when it begins, as well as signs and symptoms during and immediately after the ictus offer clues as to the type of the attack and therefore the correct diagnosis.[32] Syncope is often initiated with fading vision into black, often accompanied by dizziness, followed by a loss of

consciousness. Syncope can be associated with one or more irregular jerks or even convulsive activity, leading to ambiguity in diagnosis, and often lasts for less than 30 sec with a quick postictal recovery.[32,33] Functional seizures are characterised by paroxysmal movements, sensations, or behaviours that might look like epileptic seizures, but are not associated with ictal epileptic discharges on the EEG. When interpreting the ictal signs and symptoms, it is necessary to understand that no single sign or symptom is pathognomonic for functional seizures. However, some signs and symptoms are strongly associated with functional seizures and are infrequently seen in epileptic seizures.[34] Preictal headache, eye closure during the seizure, wax and wane motor activity, side-to-side head movements, and pelvic thrusting are symptoms or signs that are strongly suggestive of functional seizures. A functional seizure often lasts for more than 3 min and the postictal recovery is usually slow.[33,35,36] It is noteworthy to remember that a patient might have comorbid conditions such as epilepsy and functional seizures, making the diagnosis of either condition more challenging.[37]

When a diagnosis of epilepsy is made, a detailed clinical history will be key to further classify an epilepsy type or syndrome (figure 2). It is important to ask the patient and their caregivers about the age at seizure onset and the course of the illness (eg, if there was a preceding febrile illness), aura type and description (ask the patient), ictal events (ask the patient and their caregivers), and postictal events (ask the patient and their caregivers). Epileptic seizures often last for less than 2 min. Many patients have more than one seizure type and this should be inquired about carefully. It is necessary to consider that home videos of the seizures might be more helpful in picking up semiological signs and classifying epilepsy types than the history provided by the patient and their caregivers.[38] It is important to instruct the caregivers to record a seizure with their mobile phone camera, if they can. It is also important to inquire about the sleep cycle of the individual with epilepsy (eg, seizures only during sleep suggest focal epilepsy), the temporal pattern of the seizures (eg, the association of seizures with the menstrual cycle), past medical history of the patient, and their family history, psychiatric history, and social history. Finally, it is also important to know the risk factors for epileptic seizures.[2]

Although a comprehensive physical examination is mandatory, most patients with epilepsy have a normal physical examination. However, it is particularly important to evaluate for skin lesions and other congenital abnormalities; for example, adenoma sebaceum is associated with tuberous sclerosis, a rare genetic disorder that is often associated with epilepsy. Other important findings during a physical examination may include focal neurological deficits.[32,33] In areas with scarce resources (such as areas with no neurologists with expertise in epilepsy), the use of validated digital apps could help make a correct diagnosis in patients with a suspicion of seizures.[39,40]

Date: Name: Gender:
Age: Age at seizure onset:

Seizure history (course of illness):

Seizure type 1.
a. Seizure description:
b. Seizure frequency:
c. Classification:

Seizure type 2.
a. Seizure description:
b. Seizure frequency:
c. Classification:

Other seizure types:

Epilepsy risk factors:
Pregnancy complications: History of CNS infection:
Development: History of significant head trauma:
Febrile convulsion: Family history of epilepsy:

Past medical history:
Drug allergies:
Medical comorbidities:
Psychiatric problems:

Social history:
Educational level: Driving: Employment:
Marital status: Tobacco: Alcohol: Illicit drugs:
Family history:
Physical examination:

Record review:
EEG:
MRI:
Labs:

Diagnosis:
Plan and recommendations:

***Figure 2*: An example of a predesigned template for data collection during the first visit of a patient with seizures**

Electroencephalography

EEG is one of the most important and helpful ancillary tests in diagnosing epilepsy, and should be ordered in all patients with a suspicion of seizures. The EEG may provide information on the presence of abnormal brain electrical activity, as well as information that helps in the classification of epilepsy type or syndrome. For example, a focal interictal spike (figure 3) suggests focal epilepsy (such as temporal lobe epilepsy), whereas a generalised spike-wave complex (see figure 3) suggests a generalised epilepsy syndrome (such as idiopathic generalised epilepsy).[41,42] A normal EEG does not exclude the clinical diagnosis of epilepsy; in about half of patients with epilepsy, a single routine EEG will be normal.[32] If the suspicion of epilepsy is high, additional EEG recordings after sleep deprivation or protracted EEG monitoring might improve the opportunity of observing waveforms associated with epilepsy.[32]

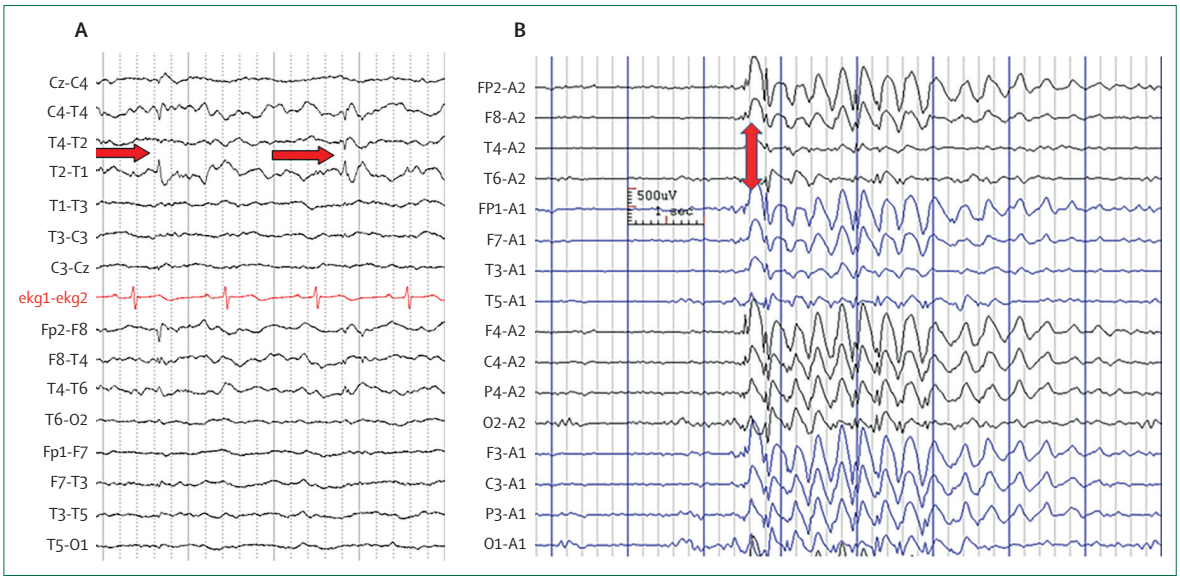

Figure 3: **EEG patterns**
(A) T2 (right anterior temporal) sharp waves in a 26-year-old woman with temporal lobe epilepsy. (B) Generalised spike-wave complexes in a 16-year-old girl with idiopathic generalised epilepsy.

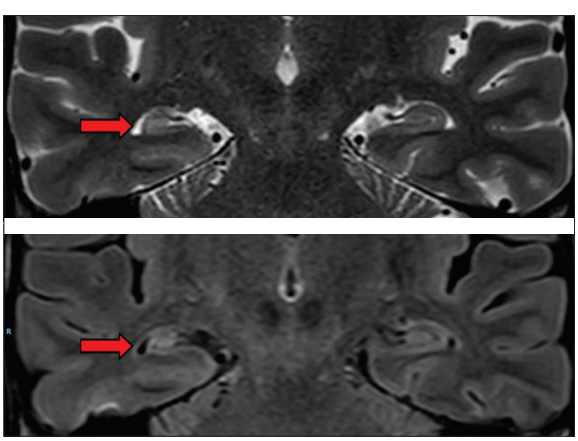

Figure 4: **Brain MRI**
Right hippocampal sclerosis in a 32-year-old man with mesial temporal lobe epilepsy.

Neuroimaging

An MRI scan of the brain is an important diagnostic tool in many patients with epilepsy. It is appropriate to obtain an MRI scan to investigate for a structural lesion if epilepsy is not believed to be idiopathic, such as juvenile myoclonic epilepsy in an adult patient. An MRI is preferable to a CT scan because it has much greater sensitivity. MRI for the evaluation of patients with epilepsy should be done using a dedicated epilepsy protocol,[43] and should be read by physicians who have experience with epilepsy.[44] An MRI might detect brain structural lesions such as tumours, cortical dysplasia, encephalomalacia, and mesial temporal sclerosis (figure 4). In a patient with uncontrolled focal seizures and a non-conclusive brain MRI by visual inspection, review by an epilepsy expert alongside voxel-based post-processing techniques could improve the yield to detect a focal lesion.[45] Emergency neuroimaging (which is often a CT scan) should be performed in all patients with a head injury (eg, as a result of a seizure), a postictal focal deficit, or change in mental status that does not quickly resolve.[32]

Autoimmune investigations

Seizures due to immunological causes represent a major challenge in neurology clinics; such seizures are increasingly encountered in clinical practice and their recognition depends on the index of suspicion. It is crucial to identify immune-related causes of seizures early in their course since they could be responsive to immunotherapy, but are usually resistant to conventional antiseizure medications.[46,47] The term autoimmune-associated epilepsy is often used to describe a condition with a long-lasting predisposition to unprovoked seizures with evidence of an immunological aetiology, such as Rasmussen's encephalitis. The term seizures secondary to autoimmune encephalitis is often used for seizures that occur as a symptom of active autoimmune encephalitis, such as anti-n-methyl-d-aspartate receptor encephalitis. In any patient with a cluster of symptoms including frequent focal seizures or status epilepticus, cognitive and memory impairments, personality and psychiatric changes, and movement disorders, one should seriously consider and investigate the possibility of seizures secondary to autoimmune encephalitis.[46]

Other investigations

Electrolytes, chemistry panels, and toxicology screening might be considered if a patient receives medical attention soon after a seizure. Lumbar puncture is

performed only if an infection or an autoimmune problem is suspected.[32]

Treatment

Antiseizure medications

Antiseizure medications represent the mainstay for the management of epilepsy. These drugs reduce the risk of seizure relapse, with little or no effect on the epileptogenesis process. Consequently, the use of antiseizure medications should be restricted to patients with a high risk of long-term seizure relapse (epilepsy). However, the decision of starting an antiseizure medication should be individualised, and can be even deferred in specific situations, for instance, if there are only very mild or infrequent seizures, with a low risk of seizure-related injuries.

Several antiseizure medications are approved for the treatment of epilepsy and their selection should rely on an evidence-based framework, integrating the best available evidence for efficacy and tolerability, risk of drug interactions and teratogenicity, presence of comorbidities, patient preferences, and costs.[48] It is important to consider the spectrum of efficacy of various antiseizure medications to avoid prescribing drugs that are inappropriate for specific epilepsy or seizure types (panel 2). Carbamazepine has been regarded as the first-choice monotherapy for focal-onset seizures for many years. Over time, randomised controlled trials have shown that various antiseizure medications (such as lamotrigine and oxcarbazepine) are non-inferior to carbamazepine.[49–51] However, the evidence from these trials is partly limited by strict inclusion and exclusion criteria with subsequent risk of poor generalisability, and by efficacy outcomes measured over time periods which are too short.[49–51] Evidence from pragmatic trials comparing the long-term effectiveness of antiseizure medications showed that lamotrigine is clinically more effective than carbamazepine, and that levetiracetam and zonisamide do not appear to be cost-effective alternatives to carbamazepine.[52] Valproic acid is an effective first-line monotherapeutic option for generalised seizures but should be avoided as a first-line drug in women of childbearing potential due to its serious teratogenic effects.[52] Although probably less effective, lamotrigine and levetiracetam appear reasonable alternatives to valproic acid (in women) due to their low risks of congenital malformations.[52,53]

In the presence of comorbidities, special attention should be given to not choosing a drug that might worsen the comorbid condition.[54] The physician should adjust the dose if liver or renal failure affects the efficacy of the antiseizure medication, and avoid drugs that could interact with other medications; where this is not possible, dose adjustments should be considered.[48] Women of childbearing age should be warned against the reduced effectiveness of oral contraception by enzyme-inducing antiseizure medications. Special attention should also be given to the older population. This is an age group where epilepsy is frequent and sometimes challenging to recognise accurately due to the wide range of diagnostic mimics (eg, syncope or transient ischaemic attacks) and chameleons (eg, post-ictal Todd's palsy due to a focal seizure misdiagnosed with acute stroke) that might lead to underdiagnosis or misdiagnosis.[55] In this specific population it is therefore crucial to start antiseizure medications only when necessary. Whenever possible, an antiseizure medication with the following properties should be chosen: linear pharmacokinetics with scarce risk of accumulation; an absence of drug-to-drug interactions; elimination through renal excretion and an absence of hepatic metabolism; and favourable tolerability profile (including on memory and cognitive performance).[55] To minimise the adverse effects, it is important to start the antiseizure medication at a low dose and to slowly increase the dose over time, if required.

Polytherapy

As a rule, pharamacological treatment should begin with a single antiseizure medication. If the first antiseizure medication does not control the seizures, considering an alternative monotherapy or combining a second medication are common therapeutic options. To our knowledge, there is no robust evidence supporting the

Panel 2: **The spectrum of clinical efficacy of some antiseizure medications**

Narrow-spectrum antiseizure medications (drugs effective primarily against focal onset seizures and focal evolving to bilateral tonic-clonic seizures)

- Carbamazepine*
- Cenobamate
- Eslicarbazepine
- Ethosuximide†
- Gabapentin
- Lacosamide
- Oxcarbazepine*
- Phenytoin*

Broad-spectrum antiseizure medications (drugs effective against both focal and generalized onset seizures)

- Clobazam
- Lamotrigine‡
- Levetiracetam
- Perampanel
- Topiramate
- Valproate
- Zonisamide

Drugs are listed in alphabetical order. The choice of antiseizure medication should not rely solely on their clinical efficacy, but also thier tolerability (including the teratogenicity in women of childbearing potential), risk of drug interactions, comorbidities, frequency of administration, patient preferences, and costs.
*These drugs might have some efficacy also against generalised onset tonic-clonic seizures, but might aggravate other generalised seizures (particularly absence seizures). †Ethosuximide is effective only against absence seizures. ‡Lamotrigine might aggravate myoclonic seizures

	Primary aims	Surgical candidates	Surgical procedures
Curative surgery	Sustained seizure freedom and improved quality of life.	Patients with drug-resistant focal epilepsy with a clearly identified epileptogenic zone* that could be removed without irreversible neurological deficit.	Resective surgery, depending on the pathology and location of the epileptogenic zone. For example, anterior temporal resection or selective amygdalohippocampectomy in hippocampal sclerosis.
Palliative surgery	Improvement in quality of life and decrease in seizure frequency or severity.	Patients with drug-resistant focal or generalised epilepsy with severe and frequent (disabling) epileptic seizures. Patients in whom seizure freedom through resective surgery is extremely unlikely.	Corpus callosotomy

*A visible lesion on neuroimaging is not always necessary: patients with focal seizures of neocortical origin and normal brain neuroimaging can still undergo successful resective surgery provided that the epileptogenic zone has been accurately identified in the presurgical evaluation.

Table: **Types of surgical approaches to drug-resistant epilepsy**

superiority of one approach over the other. Generally, an alternative monotherapy appears preferable in patients who did not tolerate the first antiseizure medication, or if the first antiseizure medication did not have any benefit in controlling seizures.[48] An adjunctive treatment is advisable if the first antiseizure medication had some effects in controlling the seizures, but failed to completely stop them.[48] If a patient continues to have seizures despite first or alternative monotherapy, adding a second antiseizure medication is usually required. Several antiseizure medications can be used in clinical practice as an adjunctive treatment for difficult-to-treat epilepsy (panel 2).[48]

Ideally, antiseizure medication polytherapy should maximise efficacy while also minimising the adverse effects (ie, a rational polytherapy).[56] Rational polytherapy could involve combining antiseizure medications with different mechanisms of action that could synergically potentiate the antiseizure efficacy of the combined drugs (eg, lamotrigine and valproate, or cannabidiol and clobazam).[57] Conversely, it is also important to avoid combinations of antiseizure medications that might worsen tolerability (eg, lacosamide added to another sodium channel blocker).[58]

Withdrawing antiseizure medications

In some patients who are seizure-free (usually for more than 2 years), or in the case of age-dependent epilepsy syndromes beyond the expected age of resolution, it is possible to consider withdrawing antiseizure medications on the basis of an accurate estimate of seizure recurrence risk and an individualised balance between the anticipated risks and benefits—this includes the possible negative psychosocial consequences of seizure relapse, such as the loss of one's driving license.[59] To our knowledge there is no robust evidence on the safest tapering regimen, although benzodiazepines and barbiturates should be withdrawn slowly.[60] In patients taking multiple antiseizure medications, one drug should be discontinued at a time.[59] In the case of seizures recurrence during or after discontinuation, the last effective withdrawn drug should be reinstated, or its dose increased back to the previous effective one. Temporary driving restrictions (eg, up to 6 months after complete treatment cessation) could be advisable.[59]

Drug-resistant epilepsy

About a third of patients continue to have seizures despite appropriate medical treatment.[49,61] This proportion has remained unchanged over the years and the overall prognosis of epilepsy has not been affected by the introduction of several new antiseizure medications.[62] Drug-resistant epilepsy is defined by the ILAE as the inability to attain sustained seizure freedom after an informative trial of two antiseizure medications that have been appropriately chosen for the individual's specific epilepsy or seizure type, used at an adequate effective dose, and tolerated.[63] Before diagnosing drug-resistant epilepsy, it is essential to rule out the potential causes of pseudo-resistance. These causes include an incorrect diagnosis of epilepsy, administration of an inappropriate drug, poor treatment adherence, or an antiseizure medication dose that is too low to provide adequate antiseizure control.[48] Several biological mechanisms have been proposed to explain drug-resistant epilepsy (pharmacokinetics hypothesis, intrinsic severity hypothesis, genetic variation hypothesis, drug transporter hypothesis, etc) and inform the development of newer antiseizure medications.[64] However, despite advances in research, the pharmacological management of patients with drug-resistant epilepsy remains challenging and often frustrating, requiring alternative therapeutic options, such as surgery.

Surgery

Surgical treatment is the most cost-effective approach for patients with drug-resistant focal epilepsy when patients carry a coherently identified epileptogenic zone that can be appropriately resected or disconnected.[65–67] A resective surgical treatment primarily aims to achieve complete seizure freedom and improve the quality of the patient's life. Epilepsy surgery can also be an option to improve the quality of life and decrease seizure severity or frequency in patients with drug-resistant focal epilepsy (who are not amenable to resective surgery), and in those with generalised epilepsy and disabling seizures; in these cases, the surgery is palliative and not aimed to achieve seizure freedom (see table).[66]

Resective epilepsy surgery requires a systematic presurgical evaluation to precisely identify the epileptogenic zone, defined as the cortical area that generates seizures and whose removal or disconnection is required for complete seizure freedom.[68] Identification of the epileptogenetic zone can be achieved by integrating information from different non-invasive and invasive

investigations, including detailed analysis of seizure semiology; video-EEG recordings; structural, functional, and metabolic neuroimaging (eg, MRI, functional MRI, [18F]fluorodeoxyglucose-PET, and single photon emission computed tomography); invasive electrical stimulation; neuropsychological testing; speech and language testing; and visual field examinations.[69] Not all of these procedures are required in every patient. Generally, less invasive procedures should be preferred over more invasive ones; for instance, stereo-EEG should be reserved for cases in which anatomical, electrical, or clinical correlations based on detailed medical history, structural imaging, and scalp EEG recording are insufficient to accurately and precisely identify the epileptogenic zone. Similarly, functional and metabolic neuroimaging should be reserved for patients where there are remaining doubts on the exact correlation and overlap between the structural lesions, the irritative zone (the area of cortex that generates interictal spikes), the ictal-onset zone (the area of the cortex that initiates clinical seizures), the symptomatogenic zone (the area of the cortex that, when activated, produces the initial ictal symptoms), the functional deficit zone (the area of the cortex that is not functioning normally in the interictal period), and the eloquent cortex.[68] The best surgical candidates are patients with focal unilateral brain lesions seen on neuroimaging, such as mesial temporal sclerosis or tumours that are correlating with the electrophysiological localisation of the seizure onset. The surgical treatment of focal seizures with non-conclusive normal neuroimaging is more challenging, due to the difficulties in defining the extent of tissue that must be removed for complete seizure abolition without causing irreversible post-surgical deficits.[66,70]

In patients with drug-resistant focal epilepsy, resective surgery is superior to long-term medical therapy alone,[71,72] with survival methods estimating sustained seizure freedom at 10 years in 47% (95% CI 42–51) of 615 adults in one study.[73] In selected cases (eg, patients with focal unilateral brain lesions seen on neuroimaging, such as mesial temporal sclerosis or tumours that correlate with the electrophysiological localisation of the seizure onset), the likelihood of achieving seizure freedom after surgery ranges from 50–80%.[67] In the presence of some highly epileptogenic lesions associated with drug-resistant epilepsy, such as focal cortical dysplasia type 2, surgical removal performed in specialised centres can lead to complete seizure freedom in over 80% of patients.[74,75] Anterior temporal resection with the removal of the temporal pole, hippocampus, and mesio-basal part of the amygdala has also shown to be efficacious in patients with unilateral mesial temporal lobe epilepsy.[76,77] In patients with unilateral mesial temporal lobe epilepsy, selective amygdalohippocampectomy, although superior to medical treatment alone in drug-resistant epilepsy, is not more effective than anterior temporal lobectomy in reducing seizures.[78] Other surgical procedures in these patients are stereotactic radiosurgery, radiofrequency ablation, and laser interstitial thermal therapy, which could cause less damage to the surrounding areas than conventional surgical approaches (eg, anterior temporal resection).[79] However, not all patients with focal epilepsy are candidates for resective brain surgery (eg, patients with non-lesional extratemporal epilepsy with an ictal-onset zone close to an eloquent cortex).

Overall, epilepsy surgery for drug-resistant focal seizures is associated with low rates of morbidity and mortality when performed at specialised centres.[66] The likelihood of postsurgical neurological deficits can be minimised by completing an accurate presurgical evaluation and selection of candidates.[80,81] Unfortunately, despite its high effectiveness for seizure control and improved quality of life, epilepsy surgery is an underutilised treatment option. A prompt referral for a surgical evaluation has been recommended in all patients with drug-resistant epilepsy as soon as drug resistance is ascertained.[65] However, too often potential candidates are not referred for a surgical evaluation due to a substantial knowledge gap on this therapeutic option.[82]

Neuromodulation

Neuromodulation techniques can be regarded as therapeutic options for patients with drug-resistant epilepsy who are not suitable for resective surgery.[83] The techniques are aimed mainly at reducing seizure frequency and severity, rather than at attaining seizure freedom. As such, neuromodulation techniques should be regarded as palliative treatments. Beyond reducing seizure frequency, these techniques could also improve the quality of life of the patients and reduce the risk of SUDEP.[83] The neuromodulation approaches evaluated in double-blind controlled trials and currently approved for the treatment of drug-resistant epilepsy are vagus nerve stimulation, deep brain stimulation of the anterior nucleus of the thalamus, and closed-loop responsive neurostimulation of the epileptic focus.[83–87]

Dietary treatments

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that mimics a starvation state. The classic ketogenic is composed of a 4:1 ratio of fat to carbohydrate and protein combined; different variants have been developed to improve palatability and adherence.[88]

The evidence for the use of the ketogenic diet in adults with epilepsy is scarce. In a 2015 meta-analysis, the pooled efficacy rate of the classic ketogenic diet was 52% (95% CI 40–64), while that of the modified Atkins diet was 34% (19–49).[89] A prospective randomised controlled trial investigated the modified Atkins diet in people with drug-resistant epilepsy aged 10–55 years; seizure reduction of greater than 50% was seen in 21 (26·2%) of the 80 participants in the intervention and two (2·5%) of the 80 participants in the control group at 6 months ($p<0·0001$).[90] The most common adverse effects associated with ketogenic diets are gastrointestinal

effects, weight loss, and derangements in lipid profiles.[88] Multivitamin and mineral supplements are useful to reduce the risk of adverse effects secondary to vitamin and mineral deficiencies.[88]

Complementary and alternative medicine

Complementary and alternative medicine consists of health-care practices that are not currently an integral part of conventional medicine.[91] Complementary and alternative medicine therapies are often used by patients with epilepsy despite the scarce and low-quality evidence to support their use.[92,93] A global survey indicated that most physicians worldwide believe that complementary and alternative medicine might be helpful to treat seizures in patients with epilepsy, but only a few reported having prescribed complementary and alternative medicine for their patients.[94] Commonly reported reasons underlying the belief in complementary and alternative medicine include inadequate seizure control and adverse effects of antiseizure medications, the comorbidities associated with epilepsy for which antiseizure medications are of little help, the perception of complementary and alternative medicine as more natural and safer than antiseizure medications, and the cost of antiseizure medications.[95] Physicians should provide appropriate information regarding the possible adverse effects of various complementary and alternative treatments, including their intrinsic proconvulsant properties, contamination by heavy metals, and risk of or interactions with the antiseizure medication.[92,93] High-quality controlled trials are warranted to provide robust evidence on the usefulness and safety of complementary and alternative medicine options in patients with epilepsy.

Panel 3: **Lifestyle considerations in patients with epilepsy**

Drug adherence

- Seizure recurrence risk in patients with epilepsy is 21% higher among non-adherers than adherers to antiseizure medications[107]
- Assessment of drug adherence should be routinely performed on every visit of patients with epilepsy[108]
- Behavioural interventions (eg, intensive reminders) might improve drug adherence in patients with epilepsy[109]
- Simplified drug regimens might also improve drug adherence in patients with epilepsy[110]

Sleep

- Patients with epilepsy are commonly advised to maintain consistent sleep routines[111]
- The sleep quality of patients with epilepsy is often disturbed due to various factors (eg, interictal epileptiform discharges, seizures, and antiseizure medications)[112]
- It is important to screen all patients with epilepsy for sleep disturbances[113]

Exercise

- Exercise has positive effects in improving cognitive functions, fitness levels, and quality of life of patients with epilepsy[114–116]

Seizure precipitants

- Stress, sleep deprivation, and fatigue are among the most common seizure precipitants reported by patients with epilepsy[117,118]
- Alcohol[119,120] and caffeinated energy drinks[121] have also been described as seizure precipitants
- Some patients have reflex epilepsy (eg, photosensitive epilepsy)[122,123]
- The treating physician should try to identify potential seizure precipitants in patients with epilepsy and help them adopt strategies for avoidance of those factors[117]
- Daily drinking of coffee and tea can be part of a healthy diet and their consumption should not be discouraged in patients with epilepsy[124]

Occupation

- Although patients with epilepsy might find most occupations manageable, it is important to follow the local rules and regulations (eg, about driving eligibility and restrictions for people with seizures)[125]
- The features of seizures (eg, fall, impaired awareness), as well as seizure frequency, should be considered when evaluating the risks associated with seizures in the workplace[126]

Diagnosis and treatment of status epilepticus

Status epilepticus is a condition defined by an ongoing and abnormally long-lasting epileptic activity, which can have negative long-term consequences, depending on the type and duration of seizures.[96] The threshold time limits for when an epileptic seizure should be considered a status epilepticus vary according to semiology, and correspond to 5 min for generalised tonic-clonic seizures, 10 min for focal status epilepticus with impaired awareness, and 10–15 min for absence status epilepticus.[96] Status epilepticus can be classified according to the presence or absence of prominent motor symptoms (the absence of prominent motor symptoms, also termed non-convulsive status epilepticus, requires EEG for the diagnosis).[96,97]

The treatment of status epilepticus should be initiated promptly to minimise the risk of negative consequences and follow a stepwise approach. Benzodiazepines represent the first-line treatment, followed by intravenous antiseizure medications (eg, fosphenytoin, levetiracetam, valproic acid, lacosamide, phenobarbital, or phenytoin).[98,99] If status epilepticus persists, anaesthetics (propofol, pentobarbital, midazolam) are usually required, with intubation and admission to the intensive care unit for further treatment and diagnostic investigation.[98] Status epilepticus that continues or recurs 24 h or more after starting anaesthetics or on the reduction or withdrawal of anaesthesia is termed super-refractory status epilepticus, which carries a high risk of mortality and morbidity. The treatment of super-refractory status epilepticus often includes the use of

immunomodulant therapies, particularly if an autoimmune cause is suspected.[100] In every stage, parallel to pharmacological treatment, it is mandatory to identify the underlying cause and treat it promptly and adequately.

Precision medicine in adult epilepsy

Precision medicine is defined as the tailoring of medical treatment to the individual characteristics of each patient.[101] Three main categories of evidence-based strategies exist to select the optimal treatment. Targeted substitutive therapies, which consist of supplementation or restriction of substrates, are used to manage epilepsies related to hereditary metabolic disorders, such as epilepsy caused by GLUT1 deficiency syndrome (ketogenic diet as the treatment option), vitamin-responsive epilepsies (such as pyridoxine [vitamin B6]-responsive epilepsy), and epilepsy caused by CLN2 disease (treated with enzyme replacement therapy using cerliponase alfa). Therapies modifying cell-signalling pathways are used to treat epilepsies related to the mTOR and immune pathways (eg, everolimus in tuberous sclerosis complex). Function-based therapies can be used to treat epilepsies caused by pathogenic variants resulting in a gain or loss of function of ion channels;[101,102] for example, antiseizure medications that block sodium channels (eg, phenytoin) might exacerbate seizures in patients with Dravet syndrome caused by loss of function variants in *SCN1A*, however are optimal for treatment of gain of function variants in *SCN2A*.[103,104] Preclinical and clinical studies of antisense oligonucleotides, a treatment capable of altering the expression of mRNA, are underway and other promising gene-based approaches such as gene editing are on the horizon.[105]

Beyond targeted therapy, personalised medicine should consider other information such as pharmacogenomic data. For example, the *HLA-B*15:02* or *HLA-A*31:01* alleles, which are common among individuals from South Asian ethnic groups, increase the risk of developing carbamazepine-induced hypersensitivity reactions like Stevens-Johnson syndrome.[106] Also, individuals with *CYP2C9* polymorphisms that reduce the activity of this enzyme can have altered metabolism of phenytoin resulting in increased serum concentrations and a greater risk of adverse effects.[106]

Lifestyle considerations

After receiving a correct diagnosis and an appropriate treatment plan, patients with epilepsy need to consider some lifestyle advice to be able to enjoy their life to its full potential (panel 3).[107–126] This advice might not only help with maintaining a seizure-free status, but also could improve patients' quality of life.

Prevention

Epilepsy prevention is one of the greatest unmet needs in neurology. Approximately 20% of all epilepsies are caused by acquired CNS insults such as traumatic brain injury, stroke, or encephalitis.[127] Mass public health interventions and programmes including appropriate maternal and child health-care plans, immunisations, and brain injury and stroke prevention strategies have the potential, therefore, to reduce the burden of epilepsy around the world.[128]

Some epilepsy-related deaths are also potentially preventable. For example, attaining seizure freedom through effective medical or surgical treatment strategies, nocturnal supervision strategies such as listening devices, and suicide prevention programmes could reduce the risk of a subset of epilepsy-related deaths.[4,20]

Future directions

There have been substantial developments in the diagnosis and management of epilepsy in the last two decades. Some of the new diagnostic and treatment prospects that are under clinical implementation include the development of wearable devices for automatic seizure detection, less invasive surgical techniques with selective ablation of the epileptogenic zone like the laser interstitial thermal therapy, and precision medicine based on the genetic cause of epilepsies. The improvement in the understanding of the pathophysiological mechanisms underpinning epilepsies might prompt the development of new agents or therapies directed to modify, or even cure, the disease as well as control the symptoms. Gene therapy and other gene-based approaches are still experimental. In gene-related epilepsy, the ultimate goal is to correct the pathogenic genetic variants or modulate the expression of the mutated gene. Basic research is also addressing agents that are able to interfere with the expression of endogenous molecules and optogenetic tools for modulating the epileptic networks, among other innovative ways to help patients with epilepsy.

Contributors

AAA-P was responsible for conceptulising the manuscript. All authors contributed to the preparation of the manuscript.

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