



## Epilepsy: new advances

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Epilepsy affects 65 million people worldwide and entails a major burden in seizure-related disability, mortality, comorbidities, stigma, and costs. In the past decade, important advances have been made in the understanding of the pathophysiological mechanisms of the disease and factors affecting its prognosis. These advances have translated into new conceptual and operational definitions of epilepsy in addition to revised criteria and terminology for its diagnosis and classification. Although the number of available antiepileptic drugs has increased substantially during the past 20 years, about a third of patients remain resistant to medical treatment. Despite improved effectiveness of surgical procedures, with more than half of operated patients achieving long-term freedom from seizures, epilepsy surgery is still done in a small subset of drug-resistant patients. The lives of most people with epilepsy continue to be adversely affected by gaps in knowledge, diagnosis, treatment, advocacy, education, legislation, and research. Concerted actions to address these challenges are urgently needed.

### Introduction

With 65 million people affected worldwide, epilepsy is the most common, chronic, serious neurological disease.<sup>1</sup> People with epilepsy suffer from discrimination, misunderstanding, social stigma,<sup>2</sup> and the stress of living with a chronic unpredictable disease that can lead to loss of autonomy for activities of daily living. Although epilepsy can be successfully treated in most cases, the treatment gap is enormous, especially in low-income and middle-income countries,<sup>3</sup> because antiepileptic drugs are inaccessible or too expensive.<sup>4</sup> Nevertheless, not all patients respond to available medical treatments, with increasing evidence that surgery and other treatments (eg, neurostimulation and diet) can be beneficial. Key features of epilepsy in children<sup>5</sup> and adults<sup>6</sup> were discussed in two previous Seminars. Here, we focus on new advances.

### Terminology

#### Definitions

An epileptic seizure is defined by the International League against Epilepsy (ILAE) as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”.<sup>7</sup> Epilepsy is characterised conceptually as an “enduring predisposition of the brain to generate epileptic seizures, with neurobiologic, cognitive, psychological, and social consequences”.<sup>7</sup>

Because the conceptual definition can be difficult to apply in everyday practice, the ILAE has now finalised an operational definition that is more suitable for clinical use.<sup>8</sup> According to the operational definition, epilepsy can be thought to be present when any of the following conditions are met: “(i) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%) occurring over the next 10 years; and (iii) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past

the applicable age or those who have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last 5 years.”<sup>8</sup> This definition maintains the distinction between unprovoked and provoked non-reflex (or acute symptomatic) seizures, which are seizures provoked by factors that temporarily reduce the seizure threshold and are not associated with an enduring predisposition and thus do not qualify for a diagnosis of epilepsy. Examples of such seizures are those occurring within 7 days of stroke or head trauma, or in conjunction with a metabolic derangement.<sup>9</sup>

#### Classification

Many attempts have been made to organise and classify seizures and epilepsies.<sup>10,11</sup> In view of the scientific advances in the past decades, in 2010 the ILAE Commission on Classification and Terminology proposed changes in nomenclature and approach (panel 1), which involve a flexible multidimensional framework,<sup>12</sup> details of which are still evolving on the basis of input from the epilepsy community.<sup>13</sup> According to the proposal, “focal” has replaced the term “partial” for seizures originating within neuronal networks limited to one cerebral hemisphere. Focal seizures are no longer dichotomised into simple versus complex on the basis of presumed changes in the level of consciousness, and a diagnosis of focal seizure should be considered whenever there are focal symptoms and signs even if a person has bilateral motor manifestations. Generalised seizures are thought to originate within bilaterally distributed cortical or cortical-subcortical networks that become rapidly engaged without a specific focality, and can involve cortical and subcortical structures, but not necessarily the entire cortex. Although many syndromes can include both focal and generalised seizure types, every effort should be made to establish whether epilepsy is the result of focal pathology, because it can have implications for surgical options.

In the 2010 ILAE proposal, the causes of the epilepsy, previously classified as idiopathic, symptomatic, or cryptogenic,<sup>11</sup> are replaced by the following categories: genetic, reserved for epilepsies for which genetic factors

have a major role in the causation of the individual's disorder and in which the causative or susceptibility genes are inherited (with Mendelian, mitochondrial, or complex patterns of inheritance) or result from de-novo mutations that might or might not be further inherited; structural or metabolic, in which there is a distinct genetically or non-genetically determined cause that is structural or metabolic (eg, stroke, trauma, brain tumour, cortical malformations, aminoacidopathies); and unknown.<sup>14</sup> A further refinement under discussion extends the structural or metabolic category to include immune and infectious causes.<sup>14</sup> Because of the complexities involved, a major challenge is the provision of a classification scheme that not only communicates advances in knowledge but can also be understood and used by the wider community, including non-epileptologists.

## Epidemiology and prognosis

### Incidence and prevalence

The prevalence of active epilepsy is 5–8 per 1000 population in high-income countries<sup>113</sup> and 10 per 1000 population in low-income countries, where even higher rates have been reported in rural areas.<sup>15</sup> These regional differences probably result from differences in risk factors for epilepsy, including infections and inadequate antenatal and perinatal care.<sup>16</sup> Similar differences exist for the incidence of epilepsy: findings from a 2011 meta-analysis<sup>17</sup> showed that annual incidence is 45 per 100 000 population (IQR 30–67) in high-income countries and 82 per 100 000 population (28–240) in low-income and middle-income countries.

### Mortality

Life expectancy has been reported to be reduced by up to 2 years in patients with cryptogenic or idiopathic epilepsies (which in the 2010 ILAE terminology correspond to epilepsies with unknown cause and some forms of genetic epilepsies), and by up to 10 years in patients with symptomatic epilepsy (epilepsies with a structural or metabolic cause, according to the 2010 terminology).<sup>18</sup> However, not all forms of epilepsy are associated with reduced life expectancy, and no evidence exists for increased mortality in self-remitting syndromes such as childhood absence epilepsy and self-limited childhood epilepsy with centrotemporal spikes.

The overall mortality rate among people with epilepsy in high-income countries is two to five times higher than in the general population,<sup>19</sup> but it can be increased by a major extent (up to 37 times) in low-income countries, especially in young people (age range 10–29 years).<sup>20</sup> Excess mortality is highest during the first years after seizure onset, mainly related to underlying causes of epilepsy and comorbidities and for young people partly because of lower mortality from other causes. In a Swedish nationwide study,<sup>21</sup> odds ratios (ORs) for premature mortality for people with epilepsy up to 54 years of age were 11.1 (95% CI 10.6–11.6) compared

### Panel 1: Proposed ILAE terminology and organisation of epileptic seizures<sup>11</sup>

#### Generalised seizures (arising within and rapidly engaging bilaterally distributed networks)

- Tonic-clonic
- Absence
  - Typical
  - Absence with special features (myoclonic absence, eyelid myoclonia)
- Atypical
- Clonic
- Tonic
- Atonic
- Myoclonic
  - Myoclonic
  - Myoclonic-atonic
  - Myoclonic-tonic

#### Focal seizures (originating within networks limited to one hemisphere)

Characterised according to one or more features:

- Aura
- Motor
- Autonomic
- Awareness and responsiveness (altered [dyscognitive] or retained)

Can evolve to bilateral convulsive seizure

#### Unknown (insufficient evidence to characterise as focal, generalised, or both)

- Epileptic spasms
- Other

with the general population and 11.4 (10.4–12.5) compared with unaffected siblings. Presence of psychiatric comorbidity contributed to increased mortality.<sup>21</sup> The causes for this excess mortality vary: although drowning and status epilepticus are leading seizure-related causes in rural China,<sup>20</sup> sudden unexpected death in epilepsy (SUDEP)<sup>22</sup> is the most common cause in high-income countries.<sup>23</sup>

The incidence of SUDEP varies across populations, from 0.1 per 1000 person-years in population-based cohorts of newly diagnosed patients to 2–5 per 1000 person-years in chronic epilepsy and up to 9 per 1000 among candidates for epilepsy surgery.<sup>23</sup> In a combined analysis of four case-control studies,<sup>24</sup> poor control of generalised tonic-clonic seizures (GTCS) was the main risk factor, with a seven-times increased risk in patients having any GTCS in a given year compared with those having none. Onset of epilepsy before 16 years of age and long duration (>15 years) were other risk factors.<sup>24</sup> In young people, epilepsy is associated with a 16–24 times increased risk of sudden death from a very low absolute risk in the general population,<sup>25</sup> with sudden death accounting for 38% of all deaths after 40 years of follow-up

in a cohort of childhood-onset epilepsy.<sup>26</sup> In childhood-onset epilepsy, SUDEP occurs mainly in patients who are not in remission and in those with a known cause of their epilepsy, and it rarely occurs before adulthood.<sup>26,27</sup>

The mechanisms of SUDEP are unknown. A survey of SUDEP cases occurring during video-electroencephalogram (video-EEG) monitoring identified a pattern in which a GTCS was followed within minutes by respiratory and cardiac dysfunction.<sup>28</sup> Although the factors that transform a GTCS into a fatal event are unknown, complete control of GTCS seems to be the most logical approach to SUDEP prevention. Indeed, findings from a meta-analysis<sup>29</sup> of randomised trials in refractory epilepsy reported a greatly decreased risk of SUDEP (OR 0.17, 95% CI 0.05–0.57) in patients randomly assigned to receive active adjunctive treatment with antiepileptic drugs compared with placebo,<sup>29</sup> a finding that lends support to the use of novel trial designs to minimise duration of placebo exposure.

### Comorbidities

Comorbidities add to the burden of epilepsy and have implications for drug selection and prognosis. For example, psychiatric comorbidity predicts worse response to initial treatment with antiepileptic drugs,<sup>30</sup> and is associated with increased risk of death.<sup>21</sup> In a population-based study,<sup>31</sup> almost a third of people with epilepsy had a diagnosis of anxiety or depressive disorder, twice the prevalence in the general population. Somatic comorbidities are also common.<sup>32</sup> Comorbidities can be causative (eg, a cerebrovascular disease causing epilepsy) or resultant (ie, epilepsy or its treatment causing a comorbidity, such as an antiepileptic drug inducing depression or obesity), or epilepsy and the comorbidity can share an underlying cause, as in the case of depression and other psychiatric disorders.<sup>32</sup> Some psychiatric comorbidities are risk factors for development of epilepsy, and epilepsy increases the probabilities for development of psychiatric comorbidities, which suggests shared causes and mechanisms.<sup>33,34</sup>

### Pathophysiology

An epileptic seizure results from transient abnormal synchronisation of neurons in the brain that disrupts normal patterns of neuronal communication and results in waxing and waning electrical discharges in the EEG (electrographic seizure). This disruption can produce various symptoms and signs that depend on the site of origin of the seizure (epileptic focus or zone) and its connections. Within the epileptic focus, seizures are often assumed to originate from increased excitation or decreased inhibition, based on a model that involves communication between two neurons where the activity of the second (final) neuron has a measurable outcome—ie, a movement in the case of a motor neuron (figure). This minimalistic model should be expanded to account for the presence of neuronal networks either

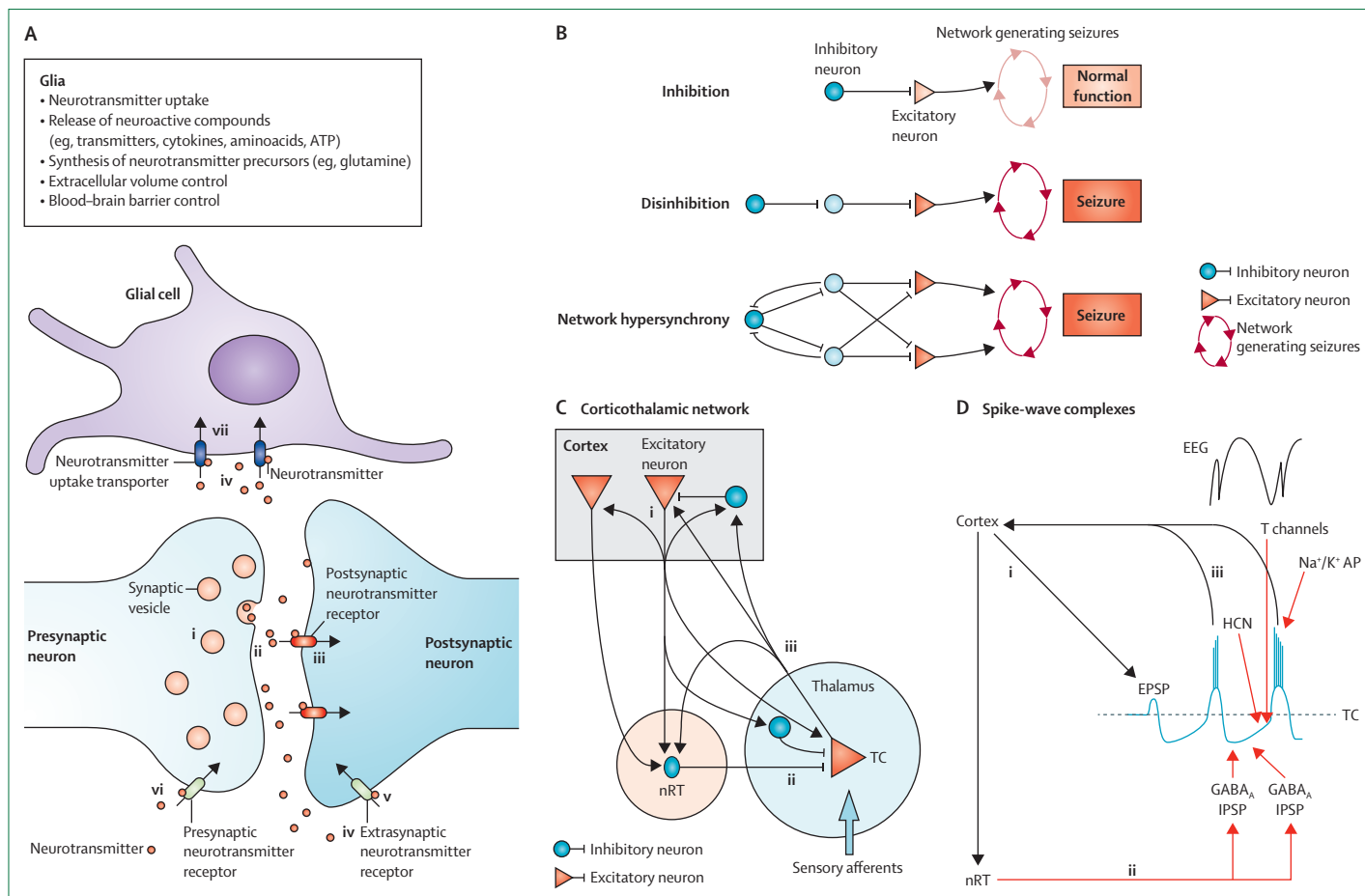
within a structure (hippocampal or neocortical networks)<sup>35–38</sup> or as cortico-thalamic and basal ganglia networks.<sup>12,39,40</sup> The interconnectivity between networks allows for coordination of different tasks and behaviours, which can provide epilepsy with its wide range of comorbidities such as depression, learning disabilities, and autistic features. Advances in video recording, neurophysiology, and imaging in animals and human beings have improved our ability to identify the brain regions involved in the epileptic focus, to establish whether seizures are focal or generalised from the start, and to define their propagation patterns.<sup>41,42</sup>

Different networks can be involved in the initiation, spread, or termination of seizures. Identification of subcortical structures involved in seizure modulation is important to design site-specific therapeutic interventions, such as deep brain stimulation. Because epilepsy networks undergo plastic changes through development in region-specific, sex-specific, and age-specific ways, the specific functions of the brain during the lifespan need to be considered.<sup>40,43</sup> For example, in rodents, depolarisation as a result of activation of GABA<sub>A</sub> receptors can be normal for the first 2–3 weeks postnatally, but it can be considered pathological in older animals. The asynchronous maturation of their different components can contribute to the increased susceptibility of the developing brain to seizures. Epigenetic factors (such as stress, seizures themselves, inflammation, and drugs) can further alter network dynamics by interfering both with signalling pathways and with brain development.<sup>40,44</sup>

Several animal models are available to study the multiple causes of epilepsy, the emergence of individual seizures (ictogenesis), and the chronic age-dependent changes involved in epileptogenesis, which lead to the development of recurrent seizures with variable response to interventions and final outcome (remission, cure, intractability).<sup>45</sup> Advances in imaging (optogenetics, tracers, multicellular calcium imaging with multiphoton and confocal microscopy, and voltage-sensitive dye imaging using epifluorescence microscopy) and electrophysiology can unravel ways by which networks are altered by epilepsy either at the whole-brain level or at the level of local circuits, and can be used to identify biomarkers to predict the development of epilepsy, identify the presence of tissue capable of generating spontaneous seizures, and measure progression.<sup>46</sup>

### Diagnosis

Diagnosis of the epileptic nature of a seizure can be based on a precise systematic description of the episode by the patient and witnesses, and might not need any specific investigation. The most important recent advance stems from the availability of smartphones, with which relatives can video-record the seizures. Unfortunately, many doctors lack knowledge of the semiology that allows differentiation between epileptic seizures and other disorders such as



**Figure: Basic elements of a seizure generating (ictogenic) network**

(A) Modulation of neuronal excitability occurs after neurotransmitters released from the synaptic vesicles are exocytosed from the presynaptic membranes (i) into the synaptic cleft (ii) and directly activate postsynaptic receptors (iii). Neurotransmitters can also leak into the extrasynaptic space (iv) activating extrasynaptic receptors (v) or can regulate presynaptic release of neurotransmitters via presynaptic receptors (vi). Glial cells are also important in neuromodulation via different actions: uptake of released neurotransmitters (vii), release of neuroactive compounds (eg, cytokines, neurotransmitters, ATP, aminoacids), synthesis of neurotransmitter precursors (eg, glutamine), control of extracellular volume (eg, via aquaporins), and control of blood-brain barrier. Increased excitation or decreased inhibition can lead to a seizure. (B) Role of disinhibition in seizure-generating neuronal networks. These networks (depicted as oval orange circuits) can be located within the same or across different brain regions and are comprised of different cell types with complex intrinsic interactions. Under physiological conditions, the networks are controlled by inhibitory neurons (blue, circular neurons), allowing for normal function to ensue (normal function, top row). If these inhibitory neurons are further inhibited (cyan-coloured circular neurons), the network can become disinhibited leading to a seizure (middle row). Thus, multifaceted inter-neuronal interactions between inhibitory or excitatory neurons can lead to pathological neuronal hypersynchrony and seizures (bottom row). (C,D) The thalamo-cortical network is one of the ictogenic networks involving such complex interactions. Excitatory input from the cerebral cortex can activate GABAergic interneurons at the nucleus reticularis thalami (C and D, step i). Subsequently, nucleus reticularis thalami GABAergic neurons can inhibit thalamo-cortical neurons, producing the fast and slow inhibitory postsynaptic potentials in thalamo-cortical neurons (C and D, step ii), which correspond to the slow-wave component of the spike-wave complex. Sequential activation of hyperpolarization-activated  $K^+$  channels (HCN) and low-threshold calcium channels (T channels) in thalamo-cortical neurons leads to a calcium spike, excitatory postsynaptic potentials, and burst of action potentials in thalamo-cortical neurons (D). Subsequently, thalamo-cortical projections (C and D, step iii) further activate the cortical neurons. The synchronous burst of activation of thalamo-cortical neurons and cortical cells corresponds to the spike component of the spike-wave discharge in the EEG. EEG=electroencephalogram. EPSP=excitatory postsynaptic potential.  $Na^+/K^+$  AP=sodium-potassium action potential. nRT=nucleus reticularis thalami. TC=thalamo-cortical neuron. Modified from Galanopoulou,<sup>36</sup> by permission of Springer.

convulsive syncope and psychogenic non-epileptic attacks, resulting in much misdiagnosis.<sup>47,48</sup> In a study<sup>47</sup> of patients previously treated for epilepsy in whom misdiagnosis was suggested after specialised neurological review, long-term monitoring with an implantable ECG recorder identified profound bradycardia or asystole in 22 of 103 patients (21%). 21 of these patients underwent pacing, and 17 of them (81%) became asymptomatic.

Correct diagnosis of the underlying epilepsy syndrome can be complex, because it needs application of multidimensional criteria and different investigations

depending on the suspected disorder.<sup>12</sup> Family and personal history, age of onset, seizure type, neurological and cognitive status, 12-lead ECG to rule out cardiac abnormalities, and an interictal EEG are mandatory. A brain MRI is generally needed, except for patients presenting with typical syndromes such as childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, or self-limited childhood epilepsy with centrotemporal spikes. Blood tests, lumbar puncture, and other investigations can be helpful when specific causes are suspected.

Major diagnostic advances over the past decade include improved imaging technology and application of epilepsy-targeted protocols for image acquisition and analysis (including three-dimensional fluid-attenuated inversion recovery and voxel-based analyses of multiple contrasts), allowing detection of previously unrecognised subtle epileptogenic lesions; identification of new forms of autoimmune encephalitis, including those associated with anti-NMDA receptors,<sup>49</sup> anti-GABA<sub>B</sub> receptors,<sup>50</sup> and antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein (anti-Lgi-1), and contactin-associated protein-2 (anti-Caspr2);<sup>51</sup> and application of genetic advances (including array comparative genomic hybridisation, candidate epilepsy gene panels, and whole-exome sequencing), leading to discovery of new gene mutations in rare epileptic disorders (either sporadic or familial).<sup>52</sup>

## Medical treatment

### General principles

Overall, about 70% of patients achieve seizure freedom with appropriately used medical treatment (panel 2), with response rates varying in relation to epilepsy syndrome,

underlying cause, and other factors.<sup>5,6,53,54</sup> Irrespective of prognostic factors, most patients who become seizure-free respond to the initially prescribed drug.<sup>54-58</sup>

No single antiepileptic drug is ideal for first-line treatment in all patients. As recommended by the UK National Institute for Health and Care Excellence guidelines,<sup>59</sup> treatment choices should take into account seizure type (panel 3), syndrome, and other characteristics such as age, sex, and comorbidities. While established antiepileptic drugs such as carbamazepine and valproic acid remain valuable first-line options, some newer antiepileptic drugs are increasingly used as initial treatment, largely because of their perceived improved tolerability and reduced propensity to cause drug interactions (table 1).

### Patients with newly diagnosed focal seizures

Several randomised trials completed in the past 7 years have compared newer-generation and older-generation antiepileptic drugs in the treatment of newly diagnosed epilepsy. Investigators of the SANAD trial<sup>60,61</sup> enrolled 2437 patients with a history of two or more unprovoked seizures within the past year. In arm A of the study, they

#### Panel 2: Key decision steps in optimisation of antiepileptic drug therapy

##### Deciding when to start treatment

The decision to initiate antiepileptic drug therapy should be based on careful assessment of the individual risk-to-benefit ratio and patient's preference (and that of the family, for children). In most situations, a history of at least two seizures 24 h apart, in the absence of provoking factors, justifies initiation of therapy, but treatment can be indicated after a single seizure in patients at high risk for recurrence.

##### Selecting the most appropriate antiepileptic drug

Choose the drug that is most likely to control seizures while minimising the risk of adverse effects. Factors to be considered are:

- Age (neonates, infants, and elderly people)
- Sex (issues related to contraception, childbearing potential, and bone health)
- Presumed spectrum of activity against the individual's seizure type or types (panel 3)
- Adverse effect profile, including age-related and sex-related side-effects
- Drug interaction potential
- Expected effect of treatment options on any associated comorbidities
- Contraindications
- Dosing constraints (eg, need for slow titration, frequency of administration, availability of convenient formulations)
- Cost and affordability
- Individual attitudes about implications of possible seizure recurrence and the side-effects of antiepileptic drugs being considered

The patient (or patient's parents) should be informed about the importance of adhering to the prescribed treatment. To optimise adherence, an effort should be made to use a simple and convenient treatment regimen.

##### Optimising dose

Aim at the lowest possible dose which is expected to control seizures. If seizures persist or adverse effects develop, adjust dose accordingly. Review clinical response regularly.

##### Revising treatment when seizures are not controlled

Exclude non-adherence. Reassess diagnosis (is it epilepsy? Is the classification of seizure types and syndrome correct?). Consider switching gradually to an alternative monotherapy. Patients with difficult-to-control seizures might need early combination therapy. When combining antiepileptic drugs, drug interactions can require dose adjustments. Assess for possible interactions with other medicines the person is receiving. Give early consideration to alternative treatments, including epilepsy surgery. Assess comorbidities and manage as appropriate. Re-evaluate regularly the balance between therapeutic benefit and side-effects. Avoid overtreatment.

##### Managing seizure-free patients

Consider **gradual discontinuation of antiepileptic drug therapy after at least 2 years of seizure freedom**. This decision needs to be carefully individualised taking into account presence of side-effects from ongoing treatment, prognostic factors for seizure recurrence, age, driving-related issues, and other activities of daily living that stopping antiepileptic drug can interfere with, and the views of the patient or patient's parents.



### Panel 3: Efficacy spectrum of the main antiepileptic drugs in different seizure types

#### Effective against focal seizures and most generalised seizure types

##### Valproic acid

##### Benzodiazepines

- Benzodiazepines occasionally exacerbate tonic seizures, particularly after intravenous use in patients with Lennox-Gastaut syndrome.

##### Phenobarbital, primidone

- Phenobarbital and primidone are not effective against absence seizures.

##### Lamotrigine

- Lamotrigine can aggravate myoclonic seizures in some patients. The efficacy of lamotrigine is best documented against focal and secondarily generalised tonic-clonic seizures, primarily generalised tonic-clonic seizures, absence seizures, and drop attacks associated with the Lennox-Gastaut syndrome.

##### Levetiracetam

- Efficacy against tonic and atonic seizures has not been documented. The efficacy of levetiracetam is best documented against focal and secondarily generalised tonic-clonic seizures, primarily generalised tonic-clonic seizures, and myoclonic seizures.

##### Topiramate

- Efficacy against absence seizures has not been documented. The efficacy of topiramate is best documented against focal and secondarily generalised tonic-clonic seizures, primarily generalised tonic-clonic seizures, and drop attacks associated with the Lennox-Gastaut syndrome.

##### Zonisamide

- Efficacy against most generalised seizure types is poorly documented. The efficacy of zonisamide is best documented against focal and secondarily generalised tonic-clonic seizures.

##### Rufinamide

- Efficacy of rufinamide against absence and primarily generalised tonic-clonic seizures has not been documented. The efficacy of rufinamide is best documented against focal and secondarily generalised tonic-clonic seizures, and drop attacks associated with the Lennox-Gastaut syndrome.

##### Felbamate

- Efficacy against absence, myoclonic, and primarily generalised tonic-clonic seizures has not been documented. The efficacy of felbamate is best documented against focal and secondarily generalised tonic-clonic seizures, and drop attacks associated with the Lennox-Gastaut syndrome.

#### Primarily effective against focal seizures, with or without secondary generalisation

##### Carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine acetate, tiagabine

- Carbamazepine, phenytoin, and oxcarbazepine can be efficacious also against primarily generalised tonic-clonic seizures. Carbamazepine, phenytoin, oxcarbazepine, tiagabine and, presumably, eslicarbazepine acetate can precipitate or aggravate absence and myoclonic seizures.

##### Lacosamide, perampamil, retigabine

- Tentative classification. Lacosamide, retigabine, and perampamil have not been assessed in patients with primarily generalised seizures.

##### Gabapentin, pregabalin

- Gabapentin and pregabalin can precipitate or aggravate myoclonic seizures.

##### Vigabatrin

- Vigabatrin can precipitate or aggravate myoclonic seizures. It is efficacious against infantile spasms.

#### Effective against absence seizures

##### Ethosuximide

- Ethosuximide can also be efficacious against myoclonic seizures.

Reported efficacy profiles reflect our interpretation of available evidence and do not necessarily imply regulatory endorsement. More detailed information about first-line and second-line AEDs for different seizure types and syndromes can be found in the National Institute for Health and Care Excellence guidelines.<sup>59</sup> Modified from Perucca,<sup>64</sup> by permission of Wiley-Blackwell.

assessed mainly patients with focal seizures and noted that, for time to treatment failure, lamotrigine was better than carbamazepine (hazard ratio [HR] 0.78, 95% CI 0.63–0.97), gabapentin (0.65, 0.52–0.80), and topiramate (0.64, 0.52–0.79), but did not offer statistically significant improvement versus oxcarbazepine (1.15, 0.86–1.54).<sup>60</sup> The advantage of lamotrigine compared with carbamazepine was mainly due to fewer patients developing unacceptable adverse effects, a difference possibly affected by the non-blinded design and use of immediate-release (rather than sustained-release) carbamazepine in an unspecified proportion of participants. In the per-protocol analysis, lamotrigine and carbamazepine did not differ in the

percentage of patients achieving 12-month remission at 2 years after randomisation.

Two other randomised, flexible-dose trials, which used a double-blind design, did not identify major differences in efficacy or tolerability between newer-generation antiepileptic drugs and sustained-release carbamazepine in the treatment of newly diagnosed focal seizures. In the first, 173 (73%) of 237 patients given levetiracetam and 171 (73%) of 235 given carbamazepine were seizure-free for 6 months or longer at the last assessed dose (adjusted absolute difference in proportions 0.2%, 95% CI –7.8% to 8.2%); withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with carbamazepine.<sup>62</sup> In the second trial, 177 (79%) of 223 of patients on zonisamide

	Advantages	Disadvantages	Selected important adverse effects*
Carbamazepine	Efficacious against focal seizures, extensive experience, mood stabiliser, low cost	Enzyme inducer; can aggravate absence and myoclonic seizures	Hypersensitivity reactions, cardiac conduction abnormalities, hyponatraemia
Ethosuximide	Efficacious against absence seizures; probably devoid of enzyme-inducing properties; low cost	Does not protect against generalised tonic-clonic seizures, which can coexist with absences in some syndromes	Hypersensitivity reactions, gastrointestinal side-effects
Gabapentin	Virtually devoid of drug interactions, relatively well tolerated, effective in neuropathic pain	Relatively modest efficacy, restricted to focal seizures; can precipitate myoclonic seizures	Weight gain
Lamotrigine	Efficacious against focal and most generalised seizure types (panel 3), devoid of enzyme inducing properties, effective in bipolar depression	Requires slow titration; dosing requirements affected by interactions with valproate, enzyme inducers, and oestrogens; can aggravate severe myoclonic epilepsy of infancy	Rash and other hypersensitivity reactions
Levetiracetam	Efficacious against focal, myoclonic, and primarily generalised tonic-clonic seizures; virtually devoid of drug interactions; relatively well tolerated	Higher cost than most other antiepileptic drugs	Irritability, mood changes
Oxcarbazepine	Similar to carbamazepine in efficacy profile, with lower risk of skin rashes and lower enzyme induction potential	Reduces blood levels of oral contraceptives; can aggravate absence and myoclonic seizures	Rash and other hypersensitivity reactions; hyponatraemia more common than with carbamazepine
Phenobarbital	Efficacious against focal and most generalised seizure types (panel 3), extensive experience, once daily dosing, low cost	Enzyme inducer; can aggravate absence seizures	Cognitive and behavioural adverse effects
Phenytoin	Efficacious against focal seizures, extensive experience, low cost	Enzyme inducer, variable and dose-dependent kinetics; can aggravate absence and myoclonic seizures	Rash and other hypersensitivity reactions; connective tissue and cosmetic adverse effects
Topiramate	Efficacious against focal and most generalised seizure types (panel 3); effective for migraine prophylaxis	Slow titration	Cognitive adverse effects, weight loss, paraesthesias, nephrolithiasis, glaucoma
Valproic acid	Unsurpassed efficacy against most generalised seizure types (panel 3); also effective against focal seizures; effective for migraine prophylaxis; mood stabiliser	Enzyme inhibitor; concerns for use in females of childbearing potential	Weight gain, adverse endocrine effects, hair loss, hepatotoxicity, pancreatitis, hair loss, greater teratogenic potential than for other antiepileptic drugs, postnatal cognitive effects after fetal exposure
Vigabatrin	Efficacious against infantile spasms	Risk-benefit ratio unfavourable outside use in infantile spasms	Irreversible visual field defects, weight gain
Zonisamide	Efficacious against focal and, probably, most generalised seizure types (table 1); devoid of enzyme inducing properties; once-daily dosing	Limited experience outside of Japan and some Pacific Rim countries	Rash and other hypersensitivity reactions, weight loss, nephrolithiasis, oligohydrosis

Modified from Perucca and Tomson.<sup>53</sup> \*The list includes some clinically significant major adverse effects which can be experienced by a fraction of patients exposed. The list is by no means exhaustive and is not meant as a comparison between the different antiepileptic drugs.

**Table 1: Some major advantages and disadvantages of potential first-line antiepileptic drugs**

compared with 195 (84%) of 233 receiving carbamazepine were seizure-free for 26 weeks or longer (−4.5%, −12.2% to 3.1%); withdrawal rates for adverse events were 11% for zonisamide and 12% for carbamazepine.<sup>63</sup> In a third double-blind trial in newly diagnosed focal seizures, 6-month seizure freedom rates were lower with pregabalin (52%) than with lamotrigine (68%; difference in proportions −16%, 95% CI −24% to −9%), but this finding should be interpreted cautiously because the trial duration was insufficient to permit dose optimisation when seizures persisted at the lowest maintenance dose (150 mg/day pregabalin, 100 mg/day lamotrigine).<sup>64</sup>

Overall, these trial findings suggest that newer antiepileptic drugs are not more efficacious than older drugs for patients with focal seizures. Additionally, their advantages in terms of tolerability can be lower than that

suggested by findings from uncontrolled studies.<sup>53</sup> Nevertheless, each of these antiepileptic drugs has a distinct profile including, for many newer drugs, lack of enzyme induction, which can justify preferential use in selected groups.<sup>53</sup>

#### **Trials in patients with newly diagnosed generalised seizures**

There are far fewer randomised monotherapy trials in generalised seizures than in focal seizures, an alarming deficiency that affects the ability to make evidence-based treatment decisions.<sup>65</sup> In the only long-term, double-blind trial ever done in a large population of children with absence epilepsy (n=453), freedom-from-failure rates at 12 months were much the same for ethosuximide (45%) and valproic acid (44%) and were much lower for

lamotrigine (21%).<sup>66</sup> Statistically, both ethosuximide and valproic acid had clear superiority over lamotrigine for this endpoint (ethosuximide OR 3.08, 95% CI 1.81–5.3; valproic acid, 2.88, 1.68–5.02). Most treatment failures for lack of efficacy were in the lamotrigine group (80 of 125), whereas discontinuations for adverse events were mostly in the valproic acid group (48 of 115). The valproic acid group also had the highest rate of attention dysfunction,<sup>66,67</sup> leading the investigators to conclude that ethosuximide is the drug of choice for childhood absence epilepsy.

In SANAD's arm B, which enrolled mostly patients with generalised or unclassified epilepsy syndromes, valproic acid was better than topiramate in time to treatment failure (HR 1.57, 95% CI 1.19–2.08) and to lamotrigine in time to 12-month remission (0.76, 0.62–0.94).<sup>61</sup> In patients with idiopathic generalised (genetic) epilepsies, the superiority of valproic acid over lamotrigine was shown both for time to treatment failure (1.55, 1.7–2.24) and time to 12-month remission (0.68, 0.53–0.89). The investigators concluded that "valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies". Caution, however, was voiced for women of childbearing potential, for whom valproic acid fetal toxicity can justify

preferential use of alternative drugs (eg, levetiracetam or lamotrigine). Evidence from prospective registries has shown that valproic acid has greater teratogenic potential than do other antiepileptic drugs, particularly at intermediate to high doses.<sup>68,69</sup> Prenatal exposure to valproic acid can also dose-dependently reduce cognitive abilities across various domains<sup>70</sup> and, possibly, increase the risk of development of autism spectrum disorder and childhood autism.<sup>71</sup>

### Drug-resistant epilepsy

In patients who did not respond to the initial antiepileptic drug, the probability of response decreases proportionally with the number of other antiepileptic drugs unsuccessfully tried.<sup>55–58</sup> On the basis of this observation, the ILAE defined drug-resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules.<sup>72</sup> In a cohort of patients with drug-resistant epilepsy (defined slightly differently as having failed at least two antiepileptic drugs, with at least one seizure per month for the previous 3 months), 5% per year entered 12-month seizure remission during long-term follow-up, but the risk of relapse after remission was 71% at 5 years.<sup>73</sup>

The relative merits of combination therapy in patients who did not achieve seizure freedom on one or more

	Primary mechanism of action	Approved indication (European Union)	Effective maintenance daily dose	Comment*
Eslicarbazepine acetate	Blockade of voltage-dependent sodium channels	Adjunctive therapy of focal seizures with or without secondary generalisation in adults	800–1200 mg once daily	Pro-drug of eslicarbazepine, the primary active metabolite of oxcarbazepine
Lacosamide	Enhancement of slow inactivation of voltage-dependent sodium channels	Adjunctive therapy of focal seizures with or without secondary generalisation in patients aged $\geq 16$ years	200–400 mg/day in two divided daily doses	Low potential for pharmacokinetic drug interactions; preliminary data suggest improved tolerability when combined with non-sodium channel blockers; also available as parenteral formulation
Perampanel	Non-competitive antagonist of glutamatergic AMPA receptors	Adjunctive therapy of focal seizures with or without secondary generalisation in patients aged $> 12$ years	4–12 mg once daily	Serum perampanel levels are reduced two to three fold by carbamazepine, phenytoin, and oxcarbazepine; approved for once-daily dosing
Retigabine (also known as ezogabine)	Enhancement of neuronal M-type potassium currents mediated by Kv7 channels	Adjunctive therapy of drug-resistant focal seizures with or without secondary generalisation in patients aged $\geq 18$ years, when other appropriate drug combinations have proved inadequate or have not been tolerated	600–1200 mg/day in three divided daily doses	Discoloration of the ocular tissues (including the retina), skin, lips and nails have been reported at high rates in long-term studies; as a result, retigabine should be regarded as a drug of last resort and ophthalmological testing is needed before and during use
Rufinamide	Blockade of voltage-dependent sodium channels	Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome in patients aged $\geq 4$ years	Variable based on age and comedication; given twice daily	Serum rufinamide concentrations are increased by valproic acid, particularly in younger children; rufinamide is an inducer of cytochrome CYP3A4
Stiripentol	Enhancement of GABA-ergic transmission	Adjunctive therapy, in combination with clobazam and valproate, of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy	50 mg/day in two or three divided daily doses	Stiripentol inhibits the metabolism of many concomitant antiepileptic drugs, which can require adjustments in dose

For further information, refer to recent reviews.<sup>87–89</sup> AMPA= $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid. \*Refer to prescribing information for more details, including adverse effects.

**Table 2: Antiepileptic drugs introduced in the market after 2006**



	Assessment	In favour of surgery	Against surgery	Notes
Seizure type	Description by patient or observer; video, EEG	Focal only (including secondary generalised seizures)	Generalised, mixed, or uncertain	Epilepsy surgery can be proposed for some rare patients with mixed seizure types with the aim of controlling focal seizures only; callosotomy can also be proposed for patients with generalised tonic or atonic seizures to decrease the risk of traumatic falls
Cause	History, MRI, EEG, genetic testing	Structural cause proven or highly suspected	Genetic (non-structural) or metabolic cause proven or suspected	Very rare patients with autosomal dominant epilepsy characterised by focal seizures (nocturnal hypermotor seizures, temporal seizures with auditory aura) have been operated on, with low success rates
Response to antiepileptic drugs	Persistence of seizures on antiepileptic drug therapy	Demonstrated lack of efficacy of at least two appropriate adequately used antiepileptic drugs	Drug responsive	In some patients, seizures can only be controlled at the cost of intolerable side-effects, a situation which justifies consideration of epilepsy surgery
Impact of seizures on cognition or quality of life	Neuropsychological tests and quality-of-life assessment	Significant	Not significant	The surgical removal of several epileptogenic zones can be considered in rare situations, such as tuberous sclerosis
Location of the epileptogenic zone	Seizure semiology Scalp-EEG, MEG MRI, fMRI, PET, ictal SPECT, invasive EEG	Well localised; single; or distant from eloquent brain regions	Not localised; multiple; or within or close to eloquent brain regions	Surgical removal of several epileptogenic zones might be appropriate in rare cases; surgery can be done in the proximity of eloquent cortex provided appropriate methods are used to precisely map such cortex; surgery can also be performed on functional brain regions in some specific situations, including very young children with potential for effective plasticity and rehabilitation and patients with catastrophic epilepsy

**Table 3: Assessment methods and criteria used to determine eligibility for epilepsy surgery**

monotherapies have been debated.<sup>74</sup> Although no controlled trials have shown superiority of polytherapy compared with alternative monotherapy,<sup>75</sup> combination therapy is widely used in drug-resistant patients, and is not necessarily associated with more side-effects.<sup>76</sup> Because the pharmacological properties of available antiepileptic drugs differ, efficacy and tolerability vary depending on the specific antiepileptic drug combination being used.<sup>77</sup> Combinations of antiepileptic drugs that act primarily by blocking sodium channels (eg, carbamazepine, phenytoin, oxcarbazepine, eslicarbazepine acetate, lamotrigine, and lacosamide) seem to be more likely to produce CNS side-effects than do combinations of antiepileptic drugs acting by different mechanisms.<sup>78,79</sup> Conversely, some antiepileptic drug combinations, notably the combination of valproic acid with lamotrigine, seem to produce synergistic beneficial effects.<sup>80,81</sup>

Because sustained seizure freedom is the main determinant of quality of life,<sup>82,83</sup> that about a third of patients cannot achieve this goal is disappointing. Drug resistance remains a major challenge<sup>84</sup> and has been addressed only to a small extent by the many antiepileptic drugs that have been introduced in the past two decades,<sup>85,86</sup> or indeed in the past 7 years (table 2).

### Emergency treatments

The first-line treatment of status epilepticus is an intravenous benzodiazepine, preferably lorazepam.<sup>90</sup> There is inadequate evidence to determine which intravenous drug should be used next if seizures persist; possible options include phenytoin (or fosphenytoin), phenobarbital, valproic acid, levetiracetam, and lacosamide.<sup>91</sup>

Because failure to rapidly suppress seizure activity increases the probability of status epilepticus becoming treatment-resistant, there is scope for early seizure termination in the prehospital setting. Findings from a randomised double-blind trial<sup>92</sup> in children and adults

with prolonged (>5 min) convulsions showed that intramuscular midazolam given by paramedics is at least as safe and effective as intravenous lorazepam to suppress seizures. Of 448 patients given midazolam, 329 (73%) were seizure-free without rescue medication at arrival to hospital compared with 282 (63%) of 445 patients given lorazepam (absolute difference in proportions 10%, 95% CI 4.0–16.1). When personnel to give injections are unavailable, buccal midazolam represents a valuable option to rapidly terminate an ongoing seizure.<sup>93,94</sup>

### Surgical treatment

Surgical treatment includes resection, destruction, or disconnection of epileptic brain tissue, and neurostimulation, which can be applied to various brain structures or to cranial nerves to modulate cerebral networks generating seizures or to abort seizures once detected.

Surgical resection is offered to suitable candidates with drug-resistant focal epilepsy (table 3), about half of whom will have long-term postoperative freedom from seizures.<sup>47,95</sup> Findings from a well-designed randomised trial<sup>96</sup> that compared anterior temporal lobectomy with medical treatment in patients with temporal lobe epilepsy showed that 23 (58%) of 40 surgically treated patients were free from disabling seizures at 1-year follow-up, versus three (8%) of 40 medically treated patients. On the basis of these data, the American Academy of Neurology recommended that “patients with disabling complex partial (focal) seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center”.<sup>97</sup> Nevertheless, the number of patients operated on annually has not increased over time in the USA.<sup>98</sup> Of equal concern, the mean duration of epilepsy before surgery remains as high

as 17 years,<sup>99</sup> despite data showing that epilepsy surgery is effective when done within 2 years of adequate trials of two antiepileptic drugs,<sup>100</sup> and that a longer epilepsy duration is associated with increased risk of surgical failure.<sup>101</sup> One contributing factor to late referral might be differences in attitude between epilepsy surgery specialists and general neurologists, many of whom acknowledge ambivalence regarding surgical treatment.<sup>102</sup> An online tool was recently developed in Canada to tackle this issue through dissemination of criteria to determine appropriateness of presurgical assessment.<sup>103</sup>

Improved seizure outcomes after surgery probably result from better delineation of the epileptogenic zone, mainly because of advances in non-invasive neuroimaging and neurophysiological techniques. Previously unrecognised subtle epileptogenic focal cortical dysplasia can now be detected using 3 Tesla magnets, optimised MRI sequence, sophisticated post-processing analysis of the cerebral cortex,<sup>104</sup> or <sup>18</sup>F-fluorodesoxyglucose PET coregistered with MRI.<sup>105</sup> Techniques have been developed to map the source of interictal spikes with improved sensitivity and reliability, including electrical and magnetic source imaging with high-resolution sensors with 128 recording channels or more,<sup>106–108</sup> and functional MRI coupled with EEG.<sup>109</sup> However, many epilepsy surgery centres do not have access to all these methods, and the effectiveness of some of these techniques for seizure outcomes after surgery remains to be established.

Neuroimaging also enabled the development of non-invasive methods to reduce surgical morbidity. Memory functional MRI can be used to predict and minimise the risk of postoperative verbal memory deficit, whereas use of tractography of the optic radiations can minimise the risk of visual field defects.<sup>110,111</sup>

The effectiveness of intracranial EEG investigations, which are still needed in a subset of patients to more precisely guide the surgical resection, has also improved in the past decade. Thanks to progress in frameless robot-assisted implantation, stereo-EEG with intracerebral depth electrodes is increasingly used to define the epileptogenic zone in complex cases,<sup>112–114</sup> with a lower rate of complications than subdural grids.<sup>115</sup> Stereo-EEG also allows thermolesion of the epileptogenic tissue,<sup>116</sup> a strategy that can eradicate epileptogenic periventricular nodular heterotopia.<sup>117</sup> The use of repetitive single-pulse stimulation and recording of abnormal EEG responses at distant sites might help to better define the epileptogenic zone and assess eloquent areas.<sup>118,119</sup> High-frequency oscillations ( $\geq 80$  Hz) recorded on intracranial EEG can also contribute to identifying the epileptogenic zone.<sup>120</sup> However, whether these methods improve the probability of freedom from seizures after surgery has not been tested.

Other advances include a better understanding of the organisation of epileptic networks, including multilobar epileptogenic zone and multifocal epileptogenic lesions, which were previously unrecognised and associated with

surgical failures.<sup>121</sup> Identification of these networks and removal of the entire epileptogenic tissues in one or several surgical steps can lead to greater seizure freedom rates.<sup>122</sup> Examples include temporal plus epilepsies, which involve both the temporal lobe and neighbouring regions,<sup>123</sup> multifocal focal cortical dysplasias,<sup>124</sup> and multiple tubers in patients with tuberous sclerosis.<sup>125</sup> Gamma-knife radiosurgery has been shown to be a safe and effective alternative to resective surgery for patients with mesial temporal lobe epilepsy.<sup>126</sup>

In patients who are seizure-free after surgery, antiepileptic drugs can be gradually withdrawn, with a risk of seizure recurrence following discontinuation that was assessed in two large adult and paediatric series, and shown to be below 20%.<sup>127,128</sup> Although early drug tapering has been shown to increase that risk, long-term seizure outcomes were not affected in these studies. Because neither study included a control group randomly assigned to remain on antiepileptic drug treatment, the comparative risk of withdrawal compared with continuing drug treatment could not be established.

### Neurostimulation

Neurostimulation was mainly developed as a palliative treatment for patients with drug-resistant epilepsy who are not candidates for resective surgery. Vagus nerve stimulation is the most widely used approach, with more than 70 000 patients treated worldwide during the past 15 years, and with consistent outcome data across centres and countries showing a seizure reduction of 50% or more in more than a half of treated patients.<sup>129</sup> However, less than 5% of patients achieve seizure freedom with this treatment.<sup>129</sup> Novel techniques include transcutaneous stimulation of the vagus<sup>130</sup> and trigeminal nerve,<sup>131</sup> with encouraging results that need substantiating in further trials.

The use of deep brain stimulation is restricted to severe epilepsies. Two randomised trials assessed the effects of chronic stimulation of the anterior nucleus of the thalamus,<sup>132</sup> and of responsive cortical stimulation whereby a closed-loop implanted device delivers an electrical stimulation on the detection of abnormal electrocorticographic activity.<sup>133</sup> Both treatments proved to be effective, but with fairly small effect sizes and seizure-free rates. Specifically, for responsive cortical stimulation (the only study that reported 95% CIs for the effect size), the mean change in seizure frequency across the entire masked assessment period was  $-37.9\%$  (95% CI  $-46.7\%$  to  $-27.7\%$ ) in the active stimulation group compared with  $-17.3\%$  ( $-29.9\%$  to  $-2.3\%$ ) in the sham stimulation group ( $p=0.012$ ). During the long-term follow-up of the anterior nucleus stimulation cohort, four patients (4%) achieved seizure freedom for at least 2 years and one for more than 4 years.<sup>132</sup> At 2 years post-implantation, six patients (8%) were seizure-free for the past 3 months. Similarly, long-term follow-up of patients undergoing responsive cortical stimulation showed that

13 (7%) were seizure-free in the previous 3 months.<sup>133</sup> Further studies are needed to establish the risk-to-benefit ratio of invasive neurostimulation.

### Challenges for the future

Epilepsy is a multifaceted disease that needs a comprehensive approach. The impediments to achievement of a productive life for people with epilepsy can be conceptualised as a series of gaps that have been identified for more than 20 years, but progress towards their resolution is slow. They include gaps in knowledge, diagnosis, treatment, advocacy, education, legislation, and research. The knowledge gap refers to poor understanding among health-care professionals of the various components of epilepsy and their implications, partly because of the intrinsic complexity and heterogeneity of

the disease. The diagnosis and treatment gaps comprise the barriers to timely identification and appropriate treatment of people with epilepsy, a major issue recently addressed by the WHO's evidence-based recommendations for epilepsy care in resource-limited settings.<sup>134</sup> The advocacy gap refers to limited access to government organisations by health-care providers, patient advocates, and patients themselves. The education gap refers to lack of knowledge about epilepsy in the public, which propagates prejudice, stigma, and discrimination. Improved education will provide the background for effective legislation to protect the rights of people with epilepsy. The research gap results from scarce funding opportunities, despite the fact that, in terms of disability weight, severe epilepsy ranks fourth among 220 health states surveyed by the Global Burden of Disease study.<sup>135</sup>

#### Panel 4: Compounds and interventions under investigation as potential tools to prevent epilepsy (antiepileptogenesis) or protect against neuronal damage (neuroprotection) after various brain insults

##### Antiepileptic drugs

Some commercially available antiepileptic drugs (including phenobarbital, valproic acid, levetiracetam, ethosuximide, topiramate, and others) display activity in some animal models of antiepileptogenesis or neuroprotection in addition to antiseizure effects; no antiepileptogenic effects have been as yet demonstrated in human beings

##### Dietary treatments

The ketogenic diet shows activity in some animal models of antiepileptogenesis or neuroprotection

##### Brain cooling

Possibly acts by reducing brain inflammation, inhibiting neurotransmitter release, modifying activation-inactivation kinetics in voltage-gated ion channels, and slowing of catabolic processes; some promising data from human neuroprotection trials

##### Antioxidants and free-radical scavengers

Agents that are under investigation include lipoic acid, adenosine, melatonin, edaravone, and vitamins C and E

##### Immunosuppressive treatments and agents targeting brain (and peripheral) inflammation

Agents under investigation include neuro-immunophilins, mTOR inhibitors (rapamycin or everolimus), inhibitors of cyclooxygenase 2, anakinra, interleukin-1 receptor antagonists, minocycline, corticosteroids, and brain cooling

##### Modulators of glutamatergic transmission

Candidate actions include blockade of group I and activation of group II or III metabotropic glutamate receptor subunit, and NMDA or AMPA receptor antagonism

##### Activators of neurotrophic receptors

Candidates include fibroblast growth factor 2, brain derived neurotrophic factor, neuropeptide Y, inhibitors of TrkB kinase, erythropoietin

##### Antiapoptotic agents

Examples include corticotropin releasing hormone, minocycline, and some antiepileptic drugs

##### Brain stimulation

Multiple cortical, subcortical, and peripheral sites are under investigation with use of either electrical or magnetic stimulation

##### Agents affecting blood-brain barrier permeability

Doxycycline and minocycline, which are endowed with additional properties, are potential candidates

##### Inhibitors of mTOR pathways

Rapamycin and everolimus have antiseizure effects and inhibit epileptogenesis in animal models of tuberous sclerosis complex and some models of acquired epilepsy; some promising findings from human trials in tuberous sclerosis complex

##### Transplantation of cells

Neuronal precursor cells, embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells are under investigation

##### Suppression of respiratory alkalosis

5% CO<sub>2</sub> inhalation is being assessed in a randomised trial in children with febrile seizures

##### Other

Examples include statins, thalidomide, progesterone derivatives, montelukast

The approaches listed can act by more than one mechanism. For more information refer to recent reviews.<sup>33,342-344</sup>

Research goals should include better understanding of the processes underlying the epilepsies, the development of new strategies to prevent epilepsy for those at risk, identification of mechanisms of pharmacoresistance, and the development of more effective treatments for patients with uncontrolled seizures and disabling comorbidities, and possibly cures. Achievement of these goals could be facilitated by impressive advances in the field of epilepsy genetics, particularly in understanding of the heterogeneity of the disease. There is also a need to develop biomarkers to predict the development of epilepsy, identify the presence of tissue capable of generating spontaneous seizures, and measure progression.<sup>136,137</sup> Potential biomarkers could emerge from advances in imaging techniques, or from electrophysiological recordings aimed at improved characterisation of specific ictal patterns, interictal spikes and sharp waves, focal slowing, and high-frequency oscillations.<sup>137</sup> Changes in excitability can be measured by judicious use of stressors and, in some settings, by direct electrical or magnetic stimulation. The development of multielectrode arrays providing enhanced temporal and spatial resolution for recording seizures in animals and human beings could aid in better identification of neurons recruited to a seizure. The same arrays could also permit identification of the surrounding penumbra, which is proposed to show the contrast between the large amplitude EEG signals and the low-level firing,<sup>41,42</sup> with low-level firing still representing a possible biomarker as focal slowing. Investigators of the ongoing FEBSTAT study have identified hippocampal MRI changes and focal EEG slowing after febrile status epilepticus in children, which could turn out to be reliable predictors of the risk of developing epilepsy later in life.<sup>138,139</sup> Coregistration techniques such as EEG-functional MRI and EEG-magnetoencephalography could also be useful, for example in identification of networks involved in seizure initiation.<sup>140</sup>

These combined approaches can be used to create novel experimental models for more cost-effective screening of potential antiepileptogenic and antiseizure drugs and devices, and eventually reduce the cost of clinical trials of potential antiepileptogenic interventions by enriching the trial population with patients at high risk for developing epilepsy and by providing validated surrogate markers of therapeutic outcomes.<sup>141,142</sup> Although the search for better antiseizure drugs should continue, improved efforts are needed to identify neuroprotective and antiepileptogenic therapies in complex systems with or without genetic mutations (panel 4).<sup>44,143,144</sup>

Collaborative efforts can provide access to unique data sources and opportunities.<sup>141,142</sup> The collaboration between ILAE, the International Bureau for Epilepsy, and WHO ensures that epilepsy will remain at the forefront of diseases regarded as crucially important to combat.<sup>145</sup> For people with epilepsy, it is imperative that essential medications are readily available to all, surgery is an accessible option when medications fail, efforts to

reduce epilepsy-related mortality are prioritised, and that there is an infrastructure for the implementation of science and health services research and capacity building for improved long-term outcomes. Initiatives such as those funded by the US Patient-Centered Outcome Research Institute and other organisations will hopefully advance translation from bench to bedside, and help to bridge the many gaps affecting the life of people with epilepsy.

#### Contributors

All authors contributed equally to this work.

#### Declaration of interests

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