Epilepsy

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Abstract | Epilepsy affects all age groups and is one of the most common and most disabling neurological disorders. The accurate diagnosis of seizures is essential as some patients will be misdiagnosed with epilepsy, whereas others will receive an incorrect diagnosis. Indeed, errors in diagnosis are common, and many patients fail to receive the correct treatment, which often has severe consequences. Although many patients have seizure control using a single medication, others require multiple medications, resective surgery, neuromodulation devices or dietary therapies. In addition, one-third of patients will continue to have uncontrolled seizures. Epilepsy can substantially impair quality of life owing to seizures, comorbid mood and psychiatric disorders, cognitive deficits and adverse effects of medications. In addition, seizures can be fatal owing to direct effects on autonomic and arousal functions or owing to indirect effects such as drowning and other accidents. Deciphering the pathophysiology of epilepsy has advanced the understanding of the cellular and molecular events initiated by pathogenetic insults that transform normal circuits into epileptic circuits (epileptogenesis) and the mechanisms that generate seizures (ictogenesis). The discovery of >500 genes associated with epilepsy has led to new animal models, more precise diagnoses and, in some cases, targeted therapies.

Epilepsy is a neurological disorder that is characterized by an enduring predisposition to generate epileptic seizures and the associated cognitive, psychological and social consequences[1]. An epileptic seizure is a transient behavioural change that might be objective signs or subjective symptoms (such as loss of awareness, stiffening, jerking, a sensation that rises from the abdomen to the chest, a smell of burnt rubber or déjà vu), caused by abnormal excessive or synchronous neuronal activity in the brain. Seizure onset can be focal (when abnormal neuronal activity arises in one or more localized brain regions or hemisphere), generalized (when abnormal neuronal activity begins in a widespread distribution over both hemispheres) or of unknown onset (if the available clinical and laboratory data cannot identify whether the onset is focal or generalized). Onset is determined when there is >80% confidence about the mode of onset based on the clinical features, electroencephalography (EEG) and neuroimaging findings[2] (BOX 1; FIG. 1). Although the cause of epilepsy in many patients is unknown, seizures can be the result of almost any insult that perturbs brain function. These insults include acquired causes (for example, after stroke or traumatic brain injury), infectious diseases (such as neurocysticercosis), autoimmune diseases and genetic mutations. To date, >500 genes associated with epilepsy have been identified.

The International League Against Epilepsy Classification framework, which was revised in 2017 (REFS 2,3), is the key tool for the diagnosis of individuals presenting with seizures. The epilepsy classification framework begins with the diagnosis of the type of epileptic seizure and assumes that non-epileptic events have been ruled out (FIG. 2). Building on this with findings from EEG and imaging, an epilepsy type and, ideally, an epilepsy syndrome (a group of clinical and electrical features that together define a distinctive clinical disorder) are diagnosed. At all points during the diagnostic work up, the clinician should consider the aetiology of the patient's epilepsy and look for comorbidities, such as learning difficulties and psychiatric disorders, including depression and autism spectrum disorder.

The first-line treatment for epilepsy is anti-seizure drugs (ASDs), of which >20 drugs have been approved by the US FDA and the European Medicines Agency. However, despite the availability of many ASDs, approximately one-third of patients fail to achieve seizure control. Epilepsy surgery has the highest chance to render these patients seizure free, although only a small number of patients are eligible for surgery[4]. Indeed, most patients with drug-resistant epilepsy are not suitable for surgery, and for those in whom epilepsy surgery has failed to control seizures, neurostimulation devices, dietary therapies or clinical trials of new ASDs are alternative options.

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For many patients, seizures can remit, and some might relapse, as shown by long-term follow-up studies. In general, epilepsy is considered resolved when an individual is seizure free and older than the applicable age for an age-dependent epilepsy syndrome or, alternatively, when the person has remained seizure free for ≥10 years with no anti-seizure medication for the past 5 years[1].

This Primer discusses the epidemiology and pathophysiology of epilepsy. In addition, this Primer includes a detailed discussion of the diagnostic work-up of patients with suspected epilepsy and describes the management of both the seizures and the comorbidities of epilepsy in addition to the quality of life (QOL) issues faced by patients.

Epidemiology

Incidence and prevalence

Almost 10% of people will experience a seizure during their lives[5]. Epilepsy is the third leading contributor to the global burden of disease for neurological disorders[6] and affects 65 million people worldwide[7]. According to a meta-analysis of international studies, the prevalence of epilepsy is 6.4 cases per 1,000 persons and the annual incidence is 67.8 cases per 100,000 person-years[8]. Prevalence and incidence estimates have been calculated in many geographical regions, although studies use different methodologies and under-ascertainment is a concern, particularly in countries where the stigma associated with seizures is rampant. Both prevalence and incidence are higher in low-income and middle-income countries (LMICs) than in high-income countries[8]. This finding might partly result from a higher frequency of traffic accidents, birth injuries and neuroinfectious disorders (such as neurocysticercosis) that can cause epilepsy in LMICs[9]. In general, causes of epilepsy include structural (for example, stroke and brain tumours), genetic (for example, *SCN1A*-related epilepsies), infectious (for example, bacterial or viral brain infections), metabolic (for example, solute carrier family 2, facilitated glucose transporter member 1 (GLUT1) deficiency), immune (for example, multiple sclerosis and autoimmune encephalitis) and unknown aetiologies[3].

The incidence of epilepsy tends to be highest in younger age groups (for example, in infancy and early childhood) and older age groups (for example, more than 50–60 years of age), whereas prevalence tends to be lowest in infants and children, increases in early adulthood–midlife and decreases later in life[8]. No sex differences in incidence and prevalence were demonstrated in one systematic review[8], although some studies have demonstrated a male preponderance, possibly owing to under-reporting by women, particularly in regions where a woman with epilepsy would be marginalized or considered unmarriable if her diagnosis was known[10].

Mortality

Epilepsy can be lethal owing to the direct effects of seizures (for example, sudden unexpected death in epilepsy (BOX 2), status epilepticus, drowning, motor vehicle accidents, falls and burns) or the indirect effects of seizures (for example, aspiration pneumonia, suicide and adverse effects of ASDs or psychiatric drugs, such as obesity and cardiovascular effects)[11]. Mortality estimates in epilepsy are influenced by methodological factors, including ascertainment methods, the choice of control group and lack of adjustment for confounders (especially the presence of comorbidities). Most studies report a higher risk of premature mortality in individuals with epilepsy than in individuals without epilepsy. The standardized mortality ratio (SMR) for epilepsy is the ratio of the number of observed deaths of individuals with epilepsy to the number of expected deaths of individuals without epilepsy in a population. A weighted SMR of 2.3 for patients with epilepsy in high-income countries and an SMR of 2.6 in LMICs was demonstrated in one systematic review[12,13]. Most studies demonstrate higher SMRs in both men and women with epilepsy than in those without epilepsy, and the SMR in patients with epilepsy is often highest in the youngest individuals, particularly during the first year of life (SMR 22.3)[13]. Epilepsy of structural origin (for example, in individuals with a demonstrable brain lesion) and drug-resistant epilepsy are associated with a higher SMR[13]. In LMICs, mortality is often due to preventable causes, such as a lack of access to medical facilities, status epilepticus and drowning[12].

Mechanisms/pathophysiology

Most studies of the pathophysiology of epilepsy use animal models that mimic human epilepsy or human brain specimens and EEG. The study of epileptogenesis focuses on the cellular and molecular alterations caused by pathogenetic events that result in an active epileptic condition. These events can include brain injuries (TABLE 1) and genetic alterations (BOX 3). The study of ictogenesis investigates the causes of seizure generation and recurrence.

Animal models

Rodents with spontaneous seizures that mimic the features of human epilepsy can be used to study pathogenetic mechanisms and potential therapeutic targets of epilepsy. Acquired models of epilepsy are produced by inducing postnatal brain injuries or mimicking

infectious agents to rodents, whereas genetic models harbour spontaneous or induced genetic modifications that lead to seizures (TABLE 1). The sex, age or strain of rodents affects several factors that contribute to epileptogenesis, including the acute brain response to injury[14] or the phenotypic expression of a genetic mutation[15], therefore affecting the onset time of spontaneous seizures, seizure frequency and severity and the development of neurological comorbidities. Non-rodent species have also been used to study seizures and epilepsy. Cats and dogs with naturally occurring or induced epilepsy have been used to test ASDs and treatments[16,17]. Non-mammalian species, such as zebrafish, can be used to study epilepsy genes and drug responses. Animal models with hyperexcitability or reduced seizure thresholds without spontaneous seizures are not reviewed here as they do not reproduce the spontaneous and recurrent seizures of human epilepsy.

Data obtained from animal models are often compared with data from surgically resected or post-mortem human brain tissue and with intracerebral recordings obtained during presurgical evaluation of patients. The cross-validation of animal and human findings adds considerable value to epilepsy research because it contributes to the deeper understanding of the mechanisms of epileptogenesis and ictogenesis. Despite this, there are no clinical studies of human epileptogenesis to prove the therapeutic effects of some treatments that demonstrated efficacy in animal models. The absence of these studies is mainly due to the lack of validated biomarkers to stratify patients with a high risk of developing epilepsy after a brain insult. However, proof-of-principle clinical studies in chronic epilepsy that tested drugs used in animal models, such as, anti-inflammatory drugs, have been carried out[18].

Epileptogenesis

Epileptogenesis (BOX 1) is initiated by a pathogenetic event ('an epileptogenic insult') or a genetic alteration, although many patients have an unknown cause. The process of epileptogenesis occurs before and persists beyond the first unprovoked seizure[19,20]; this process and the frequency and severity of spontaneous seizures can progress over several weeks in animal models and

Box 1 | **Key terms**

Acute symptomatic seizures
Seizures that occur at or near the time of a systemic or brain insult[268], such as alcohol withdrawal, drug intoxication or withdrawal, central nervous system infection, metabolic derangement, traumatic brain injury or electrolyte disturbances.

Ambulatory electroencephalography
Electroencephalography (EEG) carried out in the home environment that permits longer recordings than standard EEG.

Automatisms
Unconscious behaviours that can occur during some epileptic seizures, such as lip smacking and hand fidgeting, picking or rubbing.

Clonic seizure
A seizure accompanied by rhythmic muscle jerks.

Drop attacks
Sudden falls with or without loss of consciousness. Also known as an atonic seizure.

Epileptogenesis
A multifactorial process that underlies the development and extension of brain tissue that generates spontaneous seizures.

Focal seizure
A seizure that originates in one or more localized parts of the brain.

Generalized seizure
A seizure that originates from widespread regions on both hemispheres of the brain.

Hippocampal sclerosis
Scarring and neuronal loss in the hippocampus. This pathology is commonly found in patients with temporal lobe epilepsy.

Hyperkinetic seizure
A seizure accompanied by intense motor activity.

Ictogenesis
The dynamic changes responsible for seizure onset, progression and termination and for the transition from the interictal state into seizures.

Interictal state
The period between seizures.

Interictal spike
Brief discharges that can be observed using EEG in seizure-free periods in patients with epilepsy.

Myoclonic seizure
A seizure accompanied by rapid, involuntary muscle twitches.

Paroxysmal event
Acute onset and brief duration of a symptom or sign.

Reactive gliosis
Hypertrophy and proliferation of glial cells (including astrocytes and microglial cells) in response to central nervous system injury or increased neuronal activity.

Reflex seizures
Seizures that are elicited by a specific stimulus, such as flashing lights, hot water or reading.

Remote symptomatic seizure
Seizures that occur months to years following a brain injury or event.

Sleep-deprived EEG
EEG of an individual who was prevented from falling asleep or was allowed to sleep for a considerably shorter-than-usual period the night before the EEG.

Spike and wave discharges
Wave forms that can be observed using EEG; commonly observed in patients with generalized epilepsy and animal models of absence epilepsy.

Status epilepticus
Abnormally long seizures that can occur in individuals with or without epilepsy. The seizures can be convulsive or non-convulsive.

Tonic seizure
A seizure accompanied by sustained muscle contraction.

Tonic–clonic seizure
A seizure characterized by initial muscle contraction (tonic phase), usually causing the patient to fall, followed by rhythmic muscle jerks (clonic phase).

Unprovoked seizure
A seizure occurring in the absence of a precipitating factor.

for years in humans[19,20], which provides a broad window for anti-epileptogenic therapeutic interventions. Discovering the pathogenetic alterations that occur during epileptogenesis and lead to seizure onset, recurrence and progression is essential for therapeutic innovations.

The most commonly used models to study the mechanisms of epileptogenesis mimic acquired brain injuries, such as neurotrauma, status epilepticus, infections, hypoxia or ischaemia (TABLE 1). Mechanisms of epileptogenesis include widespread alterations in both neuronal and non-neuronal cells at several levels in the brain, including genetic and epigenetic alterations and molecular and structural changes that result in the dysfunction of neuronal circuits. Most mechanisms occur during a specific time frame before the onset of spontaneous seizures, although some mechanisms persist during disease progression. Neurological dysfunction can precede the manifestation of spontaneous seizures, and some common mechanisms might underlie epilepsy and comorbidities[21]. The plethora of epileptogenic mechanisms that have been identified in animal models suggests that epileptogenesis depends on a network of interacting pathogenetic and compensatory changes (FIG. 3). Some of the alterations that have been demonstrated in multiple animal models of acquired epilepsy have been validated in brain tissue resected from patients with drug-resistant epilepsy, such as neuronal and glial plasticity and molecular mechanisms that generate a state of hyperexcitability associated with a low seizure threshold[22]. In addition, these mechanisms affect at least one relevant outcome of epilepsy, such as spontaneous seizure onset, severity or progression, histopathological changes or comorbidities.

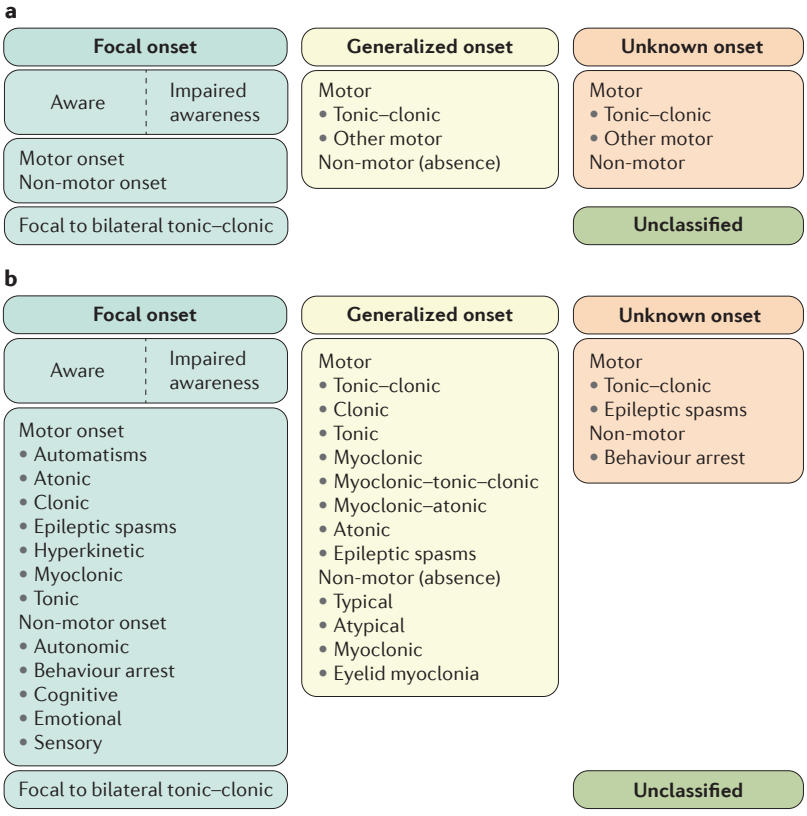

Figure 1 | **Seizure classification. a** | According to the International League Against Epilepsy 2017 basic seizure classification, which is intended for use by practitioners not specializing in epilepsy, epileptic seizures can be classified as focal onset, generalized onset or unknown onset. When possible, focal seizures are divided into seizures with preserved awareness or with impaired awareness. Focal aware seizures were previously referred to as simple partial seizures, and focal impaired awareness seizures were previously referred to as complex partial seizures. Focal-onset, generalized-onset and unknown-onset seizures can include motor and non-motor forms. Focal seizures include seizures that progress to bilateral tonic–clonic seizures (formerly referred to as secondarily generalized tonic–clonic seizures). This classification also distinguishes between bilateral seizures (which propagate to both hemispheres) and generalized seizures (which originate simultaneously in both hemispheres). **b** | The expanded seizure classification is intended for use by clinicians with expertise in the diagnosis and treatment of epilepsy. This classification has a structure similar to that of the basic classification, but the motor and non-motor categories are further divided according to features that might be present during seizures, such as automatisms and myoclonus. Adapted with permission from REF. 2, John Wiley & Sons.

Structural and morphological cellular changes. Plasticity in the dentate gyrus in temporal lobe epilepsy (TLE) with hippocampal sclerosis includes granule cell axon sprouting (also known as mossy fibre sprouting), which predominantly occurs into the inner molecular layer and hilar region and might establish excitatory feedback loops with the somata and dendrites of normal and ectopic granule cells[23]. A competing model suggests that aberrant mossy fibres innervate inhibitory basket cells located in the granule cell layer and reduce neuronal excitability[24]. Mossy fibre sprouting is likely started by the degeneration of excitatory mossy cells and the loss of inhibitory γ-aminobutyric acid (GABA)-ergic and neuropeptidergic hilar interneurons[23]. In addition, mossy fibre sprouting can be promoted by the increased expression of several factors by granule cells, such as neuromodulin (also known as growth-associated protein 43), brain-derived neurotrophic factor (BDNF), extracellular matrix proteins[25] and mechanistic target of rapamycin (mTOR) activation (see Molecular pathways, below)[26].

Mossy fibre sprouting is also linked to granule cell neurogenesis. Indeed, the developmental stage of newly born granule cells determines whether they contribute to mossy fibre sprouting after an epileptogenic injury[27,28]. In addition, granule cell neurogenesis is acutely accelerated shortly after the epileptogenic insult but is inhibited in chronic epilepsy[27]. The ectopic migration and dispersion of granule cells into the hilar region in experimental and human TLE are partly due to a loss of reelin expression, which is caused by injury of hippocampal interneurons[29]. Interestingly, the development of epilepsy and cognitive deficits are attenuated by reducing aberrant neurogenesis in rodents[30]. Mossy fibre sprouting can be suppressed in the kainic acid[31] or pilocarpine models of epilepsy[32] using rapamycin (an mTOR inhibitor), but spontaneous seizure frequency is reduced only in the kainic acid model. However, drugs that selectively blocks mossy fibre sprouting are not available, limiting data interpretation by confounding treatment effects.

Reactive gliosis occurs in the epileptogenic zone in brain tissue from patients who underwent surgery for epilepsy and in genetic and injury-induced epilepsy models[33]. Changes in glial cell phenotype are causally

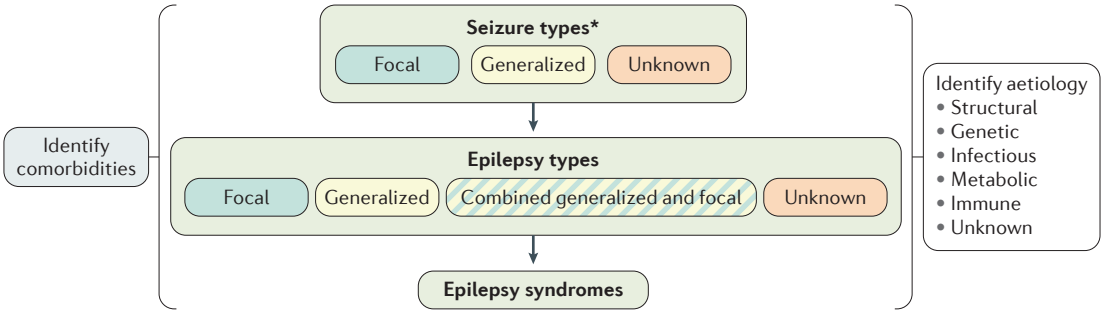

Figure 2 | **Framework for the classification of the epilepsies.** This framework begins with the diagnosis of an epileptic seizure, following which, the diagnosis of an epilepsy type and, if possible, an epilepsy syndrome. After diagnosis of an epileptic seizure, the aetiology should be identified where possible. Associated comorbidities should also be considered. * Denotes seizure onset. Adapted with permission from REF. 3, John Wiley & Sons.

linked to epileptogenesis[34,35]. Activated astrocytes have several molecular alterations that can promote neuronal network hyperexcitability, including the downregulation of gap junction connexins, glutamate transporters, potassium channels (for example, Kir4.1) and aquaporin 4 channels[33], and lead to altered neuronal expression of cation-chloride co-transporters [35]. Moreover, decreased glutamine synthetase (which converts glutamate into glutamine) activity in astrocytes disrupts the balance of glutamate and GABA in glutamatergic and GABAergic neurons throughout the brain, and increased adenosine kinase (AK) activity in astrocytes (which regulates adenosine levels by converting the purine ribonucleoside adenosine into 5′-AMP) reduces inhibitory adenosine around synapses; both mechanisms can cause spontaneous seizures[35,36]. In epileptic mice, the functional non-overlapping domain organization of astrocytes is disrupted with reactive astrocytes; this phenomenon is associated with an increased density of dendritic spines on excitatory neurons, which might contribute to hyperexcitability[37]. Finally, activated astrocytes release gliotransmitters and cytokines, which increase neuronal network synchronization[38].

Microglia activation is one of the earliest cellular events occuring during epileptogenesis and is detected within minutes of status epilepticus onset[39]. Microglia can be activated by several molecules, such as ATP, high mobility group protein B1 (HMGB1) and various neurotransmitters that are released by functionally activated viable cells or damaged cells (such as neurons, astrocytes and brain endothelial cells) and can also be activated by blood-circulating molecules or molecules imported by leukocytes across the blood–brain barrier (BBB)[39]. Microglia have been implicated in seizure-induced neurodegeneration[39], although neuronal cell loss is not required for microglial activation, as shown in non-lesional seizure models[40]. Indeed, microglial activation precedes neuron degeneration in a model of Unverricht–Lundborg progressive myoclonus epilepsy (which is caused by mutations in *CSTB*)[41]. In addition, microglial activation precedes astrocyte activation and myoclonus, suggesting a critical role for microglia in the disease pathogenesis[42]. Microglia can also activate astrocytes and modulate neuronal activity in epilepsy[39]. Reciprocal microglia–neuron signalling has been demonstrated by the release of the chemokine fractalkine by neurons, which activates microglial CXC-chemokine receptor 1 (CXCR1). CXCR1 signalling affects neurogenesis, neuronal survival and synaptic plasticity[39]. Activated microglia and astrocytes release cytokines (for example, IL-1β and tumour necrosis factor), chemokines (for example, CC-chemokine ligand 2) and danger signals (for example, HMGB1 and ATP) that lead to neuronal hyperexcitability[43,44], contributing to epileptogenesis. However, minocycline (a potent microglia inhibitor) administration had no anti-epileptogenic effects in electrical status-epilepticus-exposed rats, but reduced spatial learning deficits and attenuated spontaneous seizures and neuronal loss in pilocarpine-injected mice[45,46]. Microglia can have pathogenetic as well as restorative functions[47]; thus, the selective blockade of detrimental microglia functions is critical to try to stop epileptogenesis.

BBB dysfunction can be caused by brain vessel inflammation due to cytokines and chemokines released by activated glial cells[48] or induced in endothelial cells following AK activation[49], or by the interaction of circulating leukocytes with adhesion molecules that are upregulated on activated endothelial cells[50]. BBB dysfunction is common in acquired or structural epilepsies in animal models and patients and is associated with the development of epilepsy in animal models[51,52].

Neuroprotection does not prevent spontaneous seizures in models of epileptogenesis induced by status epilepticus or neurotrauma[53]; moreover, animal models of epilepsy (such as models of febrile seizures) can show no evidence of neurodegeneration[40], suggesting that neuronal death is not required for epileptogenesis. However, in some models of epilepsy, such as TLE with hippocampal sclerosis, cell death contributes to maladaptive plasticity in the dentate gyrus, leading to neuronal hyperexcitability.

Transcriptomic and epigenetic modifications. Genes are differentially expressed during epileptogenesis, and microarray of epileptogenic tissue from animal models has revealed common molecular pathways[20,54]. Both transcriptional and epigenetic mechanisms contribute to alterations in voltage-gated and receptor-gated ion channels during epileptogenesis. For example, the

Box 2 | **SUDEP**

Sudden unexpected death in epilepsy (SUDEP) occurs in ~1 in 1,000 adults with epilepsy[269]. SUDEP is under-ascertained, and European and North American medical examiners fail to identify SUDEP as a potential or definite cause of death in one-half to two-thirds of cases[269,270].

Individuals with generalized tonic–clonic (GTC) seizures have a tenfold increased risk of SUDEP compared with individuals without GTC seizures, whereas individuals with more than three GTC seizures per year have a 15.5-fold increased risk of SUDEP[271]. Thus, physicians must try to control GTC seizures in patients. Aside from the presence of GTC seizures, other risk factors for SUDEP with moderate to high levels of supporting evidence include a higher frequency of GTC seizures, a lack of seizure freedom for 1–5 years and being randomized to placebo instead of an active anti-seizure drug (ASD) in clinical trials for patients with drug-resistant epilepsy[272]. Factors associated with a reduced risk of SUDEP include nocturnal supervision (for example, listening or measuring bed movement) and nocturnal monitoring devices (for example, devices that detect motion or changes in electrodermal skin activity)[272].

Most cases of SUDEP follow GTC seizures during sleep, and individuals are often found in the prone position. Postulated SUDEP mechanisms include postictal suppression of brain activity and arousal associated with impaired respiratory, autonomic and cardiac function[272]. SUDEP is more common in individuals of low socioeconomic status than in those of moderate to high socioeconomic status; in a study of individuals of low socioeconomic status in Ohio, young adults with epilepsy died 16.9 years prematurely[272]. The prevention of SUDEP focuses on reducing seizures, especially GTC seizures. Studies support that reducing seizure frequency using ASDs, resective surgery or neurostimulation can reduce the incidence of SUDEP[272].

transcriptional upregulation of low threshold T-type calcium channels (such as Cav3.2 channels) during epileptogenesis increases the intrinsic burst firing of pyramidal neurons, thereby promoting seizures. By contrast, genetic deletion of *CACNA1H* (encoding Cav3.2) reduces spontaneous seizures and attenuates neuropathology in status-epilepticus-exposed mice[55], and pharmacological inhibition of T-type calcium channels by ethosuximide before the onset of absence seizures in rats decreased spike and wave discharges (SWDs; BOX 1)[56] and reduced depressive-like behaviours[57]. These therapeutic effects were associated with normalization of epileptogenic changes in voltage-gated sodium channels (such as Nav1.1 and Nav1.6) and potassium/sodium dendritic hyperpolarization-activated cyclic nucleotide-gated channel 1 channels. Mutations in sodium channels are responsible for genetic epilepsy syndromes with a wide range of severities[58], and reduction of hyperpolarization-activated cyclic nucleotide-gated channel function leads to perturbations of dendritic excitability in epilepsy[59], with both alterations contributing to seizures.

The RE1-silencing transcription factor is induced during epileptogenesis and affects the expression of genes encoding ion channels, receptors and other neuronal proteins. Blocking RE1-silencing transcription factor function attenuates epileptogenesis[60]. In addition, the Janus kinase (JAK)– signal transducers and activators of transcription (STAT) transcriptional pathway is activated during epileptogenesis and modifies the expression of genes involved in the cell cycle and survival. Inhibition of the JAK–STAT pathway decreases the severity of epilepsy in rats[61]. Other transcriptomic alterations have been described in epilepsy, although the consequence of these is poorly understood (FIG. 3).

Epigenetic mechanisms also affect gene expression during epileptogenesis and include DNA methylation, histone modification and microRNA (miRNA) expression[62,63]. DNA hypomethylation (leading to gene activation) occurs within 1 day of experimental status epilepticus whereas DNA hypermethylation (gene silencing) occurs in chronic epilepsy models and in patients with TLE[63]. In addition, broad-spectrum DNA methylation inhibitors and adenosine-induced DNA hypomethylation reduce seizure-like activity in rodent brain slices and attenuate seizure progression *in vivo*[64,65]. Histone acetylation and phosphorylation also affect the expression of genes that have a role in epileptogenesis. Indeed, histone deacetylase inhibitors (such as valproate)[66] reduce aberrant neurogenesis in the dentate gyrus and induce neuroprotection in models of status epilepticus, but their role in affecting seizure generation is controversial[63]. Finally, >100 miRNAs, including miRNAs targeting dendritic spines, neurotransmitter receptors, transcriptional regulators and inflammatory signalling, are altered during epileptogenesis in rodents and in hippocampi from patients with TLE[62,67]. Interventions with small-molecule inhibitors of miRNA (such as antagomir) or with oligonucleotides that mimic the action of miRNA in animal models demonstrated that targeting specific miRNAs, such as miR-146a, which controls the activation of the neuroinflammatory IL-1 receptor–Toll-like receptor 4 pathway[67], or miR-134, which negatively regulates dendritic spine volume[68], strongly inhibits epileptogenesis. miRNAs control broad epileptogenic pathways, but further confirmation of their precise roles in epilepsy is needed.

Molecular pathways. Several molecular pathways with potential pathogenetic or homeostatic roles are altered during epileptogenesis. Paradoxically, the same molecular pathway might have either role, depending on the time point of activation or decay and changes in the tissue microenvironment[20,22].

BDNF signalling through the BDNF/NT3 growth factors receptor (TrkB) is activated in the hippocampal mossy fibre pathway during epileptogenesis in rodents. BDNF–TrkB binding potentiates glutamatergic neurotransmission and impairs inhibitory synapse function[69]. Indeed, BDNF–TrkB signalling alters the transcription of $GABA_A$ receptor subunits in granule cells in the dentate gyrus, leading to a receptor composition that is permissive for hyperexcitability[70]. Pharmacological or chemogenetic mimicry of BDNF–TrkB signalling increased the number of seizures, whereas reduced BDNF–TrkB signalling prevents spontaneous seizures, conveys neuroprotection and rescues cognitive deficits and anxiety-like behaviours in rodent models of epilepsy[69].

mTOR signalling has a role in synaptic plasticity, neurogenesis, dendritic morphology and axonal sprouting[71]. mTOR hyperactivation has been demonstrated in patients with tuberous sclerosis complex (TSC), in genetic models of TSC and in acquired epilepsy models. In several epilepsy models, such as murine genetic TSC, absence epilepsy and post-traumatic epilepsy[72], suppressing mTOR complex 1 activity using rapamycin

reduced seizure frequency, neurological comorbidities and neuronal and glial pathology, and disrupted epileptogenesis; however, some benefits were reversed after drug discontinuation[73]. Rapamycin has limited anti-seizure effects in acute seizure tests in naive mice[74], although this drug reduces epileptic spasms in a rat model of West syndrome (an epilepsy syndrome)[75] and has anti-seizure properties in children with TSC[76].

Table 1 | **Animal models of epilepsy**

Aetiology	Rodent model	Epilepsy type
Structural		
Neurotrauma	• Fluid-percussion-induced cortical injury • Controlled cortical impact-induced injury • Cortical undercut injury	Multiple
De novo status epilepticus	• Electrical stimulation-induced, such as hippocampal or perforant path stimulation • Chemoconvulsant-induced, such as intrahippocampal, intracortical or intra-amygdala kainic acid, or systemic pilocarpine or kainic acid • Hyperthermia-induced	TLE
Stroke	• Cortical photothrombosis • Permanent middle cerebral artery occlusion • Intracortical endothelin 1	Multiple
Blood–brain barrier damage	• Cortical exposure to albumin or intracerebroventricular infusion of albumin • TGFβ1 intracerebroventricular infusion	Multiple
Developmental epileptic encephalopathies	Hypoxia–ischaemia injury in rats	Multiple
	• Multiple-hit rat model[a] • Intracortical or intrahippocampal tetrodotoxin in rats	Infantile spasms
Cortical dysplasia	• *Pten*-knockout, *Dcx*-knockout and *Otx1*-knockout mice • Knock-in of human *PAFAH1B1* (also known as *LIS1*) • *Arx* mutations in mice	Multiple
	• *In utero* rat irradiation • *In utero* alkylant agents (MAM and BCNU)	Multiple
Glioblastoma	• Neocortical transplantation of human glioma cells in SCID mice • Neocortical transplantation of glioma cell lines in rats	Multiple
Infectious		
Viral encephalitides	Theiler murine encephalomyelitis virus	TLE
Cerebral malaria	ANKA strain of *Plasmodium berghei* murine model	Multiple
Genetic or presumed genetic		
Tuberous sclerosis complex	Cell-specific conditional *Tsc1*-knockout or *Tsc2*-knockout mice	Tuberous sclerosis complex
Spontaneous mutations	• Genetic absence epilepsy rat from Strasbourg • Wistar Albino Glaxo Rijswijk rats • High-voltage spike and wave spindles in rats	Rat absence epilepsy
	• Tottering mice • Lethargic mice • Stargazer mice • Mocha 2j mice • Slow-wave mice • Ent mice • Ducky mice • *Gabrg2* conditional knock-in mutation in mice	Absence epilepsy
Induced monogenic mutations	• Knockout or knock-in mutations of voltage-gated ion channel subunits (sodium, potassium and calcium) in mice • Knockout or knock-in mutations of neurotransmitter receptor subunits ($GABA_A$ and nicotinic) and transporters • Knockout or knock-in mutations of accessory synaptic proteins • *Cstb*-knockout mice	Multiple
Developmental epileptic encephalopathies	*SCN1A* or *SCN1B* knock-in of human mutations in mice or constitutive or conditional knockout mice	Dravet syndrome
	• *ARX* knock-in of human mutations in mice or constitutive or conditional knockout mice • *Apc* conditional knockout mouse	Infantile spams
	SCN8A knock-in of human mutations in mice	Infantile spams

Models are in live animals and include both rats and mice unless otherwise indicated. BCNU, carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea); MAM, methylazoxymethanol acetate; SCID, severe combined immunodeficient; TGFβ1, transforming growth factor-β1; TLE, temporal lobe epilepsy.
[a]Multiple-hit rat model: intracerebral injections of doxorubicin and lipopolysaccharide, with or without intraperitoneal injection of *p*-chlorophenylalanine.

The efficacy of rapamycin in models of TLE is controversial[31,32]. The precise mechanism of action behind the therapeutic effects of rapamycin might depend on the animal model and aetiology.

Neurons and astrocytes are major sources of adenosine, and adenosine cellular levels are regulated by AK[77]. Adenosine has anticonvulsive properties that are mediated by adenosine A1 receptors; indeed, mice lacking adenosine A1 receptors develop lethal status epilepticus[78]. Adenosine A1 receptors are reduced in seizure-generating areas in rodent models of epilepsy, which could contribute to epileptogenesis[78]. In addition, astrogliosis is associated with persistent AK hyperactivity, which reduces adenosine levels[36]. In mice, transient delivery of adenosine to the brain after the onset of epilepsy inhibits disease progression, even after delivery of adenosine ceases[65]. In addition, the focal delivery of AK inhibitors into the epileptogenic zone or dietary interventions that reduce AK expression (such as the ketogenic diet) reduce seizures in animal models of epilepsy[36,79].

BBB dysfunction allows albumin extravasation into the central nervous system (CNS), leading to transforming growth factor-β (TGFβ) signalling in astrocytes, which causes the induction of inflammatory mediators and the downregulation of Kir4.1, aquaporin 4 and excitatory amino acid transporter 2 (GLT1, a glutamate transporter) in astrocytes[80]. Cortical astrocytes that have been exposed to albumin or TGFβ mediate excitatory synaptogenesis[52] and affect inhibitory neurons by releasing glycoproteins that interact with the extracellular matrix. Both of these effects could lead to a state of hyperexcitability[81]. Reducing TGFβ signalling reduces spontaneous seizure generation in acquired epilepsy models[51].

Increased neuronal activity or brain injury activates CNS innate immune responses that promote the production and release of inflammatory mediators[44,82]. During post-injury epileptogenesis and in some genetic epilepsy models[42], neuroinflammation is associated with oxidative stress[83]. Indeed, reactive oxygen species (generated by mitochondrial dysfunction) and increased NADPH oxidase and xanthine oxidase activity induces inflammatory genes and promotes the release of IL-1β and the redox-sensitive protein HMGB1 from activated microglia and astrocytes[84]. These molecules activate neuronal IL-1 receptor type 1 and Toll-like receptor 4, leading to hyperexcitability[85], and activate the transcription of genes involved in the neuroinflammatory cascade in glial cells. Both neuroinflammation and oxidative stress (which also includes reactive nitrogen species generated by inducible nitric oxide synthase) have been implicated in neuronal death, seizures, epileptogenesis and the comorbidities of epilepsy[44,86]. Anti-inflammatory or antioxidant therapies have demonstrated efficacy in preliminary studies in paediatric and adult treatment-resistant epilepsies[87,88].

Other mechanisms. Epileptogenesis might also be fostered by a relative deficiency of molecules that limit neuronal activation. These molecules include neuroactive peptides[89], neurosteroids from astrocytes that promote $GABA_A$ receptor inhibition[90], astrocytic sphingosine 1-phosphate receptors (which have anti-inflammatory activity)[91], erythropoietin and peroxisome proliferator-activated receptor-γ activation[92]. Deficits in these molecules are speculated to lead to hyperexcitability.

Ictogenesis

Interictal and ictal discharges (BOX 1) can be observed and recorded at high temporal resolution using neurophysiology tools and electrodes that measure population events (the activity of multiple neurons) and single neuron activity, and are ideally studied by combining electrophysiology with functional or molecular imaging and optogenetics[93]. Ictogenesis can be modelled in animals with chronic epilepsy or acute seizures using different experimental preparations that retain different degrees of brain connectivity and functionality[94]. *In vivo* experiments using epileptic animals allow limited access to brain circuitry, whereas *in vitro* seizure models are ideal for the analysis of local ictogenic networks, although electrical or pharmacological stimulation is needed to induce seizure-like activity[95]. Studies using *in vivo* and *in vitro* models of epilepsy and seizures have demonstrated substantially different ictogenic networks for focal and generalized seizures.

Generalized-onset seizures. Bilaterally synchronous SWDs are frequently observed in patients and in animal models of absence epilepsy[96]. The SWD core is sustained by thalamo-cortical networks and is generated by the resonant intrinsic membrane properties of these neurons and by interactions between neurons in the thalamo-cortical relay nuclei, nucleus reticularis thalami and the neocortex[97]. Increased calcium currents and GABA-mediated inhibition occur in thalamic neurons in genetic and acquired models of absence epilepsy[98,99]. In addition, single gene mutations in mice with generalized SWDs correlate with enhanced tonic (long-lasting)

Box 3 | **Epilepsy genetics**

Many epilepsy genes have been identified, including genes that increase the risk of different types of epilepsy, such as generalized and focal epilepsy and the developmental and epileptic encephalopathies (DEEs). The DEEs are associated with >60 genes; these genes have a role in ion channel and synaptic dysfunction, as well as transcriptional regulation, among other functions[183].

Genomic copy number variants, such as microdeletions and microduplications, cause 4% of DEEs and contribute to the aetiology of others[184]. 3% of patients with genetic (idiopathic) generalized epilepsy have a copy number variant that acts as a susceptibility allele rather than being wholly causative[273].

Focal epilepsy — which accounts for 60% of all epilepsy — can be caused by mutations in several genes, including genes encoding ion channels and genes that regulate cell growth. In particular, genes associated with the mechanistic target of rapamycin (mTOR) pathway have been implicated, and pathogenetic variants might result in both lesional (such as focal cortical dysplasia and cortical malformations) and non-lesional epilepsy. mTOR pathway genes that cause focal epilepsy include *TSC1*, *TSC2*, *MTOR* and the GATOR1 complex genes *DEPDC5*, *NPRL2* and *NPRL3* (REFS 257,274).

The main advances in epilepsy genetics have been in monogenic disorders. Most mutations occur in the protein-coding exons, which comprise ~1.5% of the genome; however, mutations in non-coding regions have been identified, including non-coding repeat expansions in familial adult myoclonic epilepsy[275], and more are likely to emerge. Whole-genome sequencing will be able to detect these variants, but analysis remains challenging and is the focus of considerable research effort.

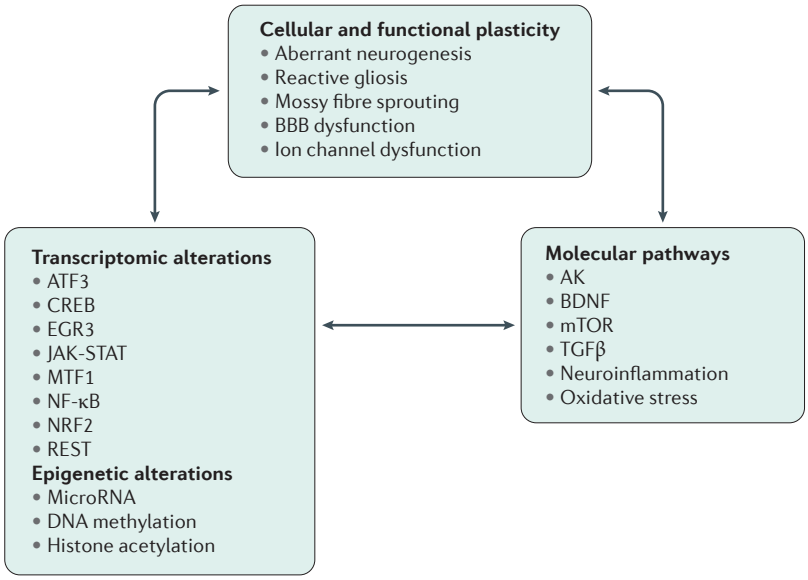

Figure 3 | **Mechanisms of epileptogenesis.** Schematic representation of the alterations that occur in the brain during epileptogenesis. These data are from animal models of acquired or genetic epilepsy. Cellular alterations include phenotypic and functional changes in neurons, glia and blood vessels, the latter of which can lead to dysregulation of the blood–brain barrier (BBB). Circulating macrophages extravasate into the brain parenchyma, contributing to inflammation and neuronal cell loss. In addition, transcriptomic and epigenetic changes, together with associated molecular pathways, contribute to ion channel and receptor modifications that are permissive for neuronal hyperexcitability. These changes decrease the seizure threshold, thereby contributing to the onset and progression of epilepsy, including the development of spontaneous seizures, cell loss and neurological comorbidities. AK, adenosine kinase; BDNF, brain-derived neurotrophic factor; CREB, cAMP-responsive element-binding protein; EGR3, early growth response protein 3; JAK, Janus kinase; MTF1, metal regulatory transcription factor 1; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-κB; NRF2, nuclear factor erythroid 2-related factor 2; REST, RE1-silencing transcription factor; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β.

GABA-mediated inhibition and de-inactivated T-type calcium channels, both of which promote thalamo-cortical loop bursting activity[100]. Limbic circuitry might also form an integral component of SWDs in typical and atypical absence seizures[101].

Multisite recordings in rat models of absence seizures demonstrated that a region of the somatosensory cortex initiates the SWD and rapidly recruits thalamo-cortical circuits[102]. The leading role of the cortex in SWD onset was confirmed by functional imaging in animal models of absence seizures[103] and in patients with generalized epilepsy[104]. Whether these ictogenic mechanisms apply to other generalized epilepsies is unknown.

Focal seizures. Focal ictogenesis can be studied either in naive brains in which acute seizures that mimick human EEG patterns are generated or in epileptic brains exposed to epileptogenic insults to reproduce human epilepsies[105]. Interictal and ictal epileptiform discharges not only rely on increased excitatory synaptic transmission and reduced inhibitory synaptic transmission but are also due to non-synaptic and non-neuronal mechanisms of synchronization[106].

The two main interictal events observed in focal epilepsy are interictal epileptiform spikes (IESs) and high-frequency oscillations (HFOs). In animal models of epilepsy, IESs are generated by enhanced excitatory synaptic transmission and by calcium spikes in principal (glutamatergic) cortical neurons[106,107]. IESs are associated with transient hyperexcitability of cortical principal neurons, followed by a slow synaptic inhibitory potential that silences principal neurons (FIG. 4), which dampens tissue excitability and has been proposed to protect against seizure generation[108]. Supporting this hypothesis, IESs induced by low-frequency stimulation prevented seizures in animal models[109] and in patients with epilepsy[110]. Whether IESs are always generated by hyperactivity of principal neurons is questioned by data from unit recordings of animal models and patients[111]. In acute seizure models, IESs that are followed by less-pronounced slow waves are not sensitive to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamatergic receptor antagonists and are sustained by the hyperactivation of GABAergic interneurons[112]. Moreover, in a model of TLE, IESs lacking the inhibitory slow wave increase in frequency during early epileptogenesis whereas spikes followed by a large slow wave decrease in frequency when spontaneous seizures emerge[113,114].

HFOs occur in epileptogenic regions in patients and might be biomarkers of epileptogenesis[115,116]. Interictal HFOs at 80–250 Hz can be sustained by both inhibitory and excitatory synaptic transmission and by non-synaptic network mechanisms in physiological conditions and in epileptic tissue[115]. Fast HFOs at 250–600 Hz are likely generated by out-of-phase firing of cortical neurons in areas of brain damage[117,118].

Overall, interictal events are generated by pathologically rearranged cortical networks that might have different functions in ictogenesis, as their role in seizure generation is still debated[108,119]. Studies of seizure onset patterns *in vivo* and *in vitro* demonstrated that increased activity in both excitatory neurons and inhibitory interneurons can initiate a seizure (FIG. 4). For example, in a rat model of mesial TLE, pathologically interconnected principal neurons fire in synchronous bursting clusters that increase in size and coalesce to generate limbic seizures with a hypersynchronous onset[120] (FIG. 4b). By contrast, in acute and chronic models, low-voltage fast activity at seizure onset correlates with interneuronal GABA-mediated network activation without the early involvement of principal neurons[121,122] (FIG. 4c). This neuronal activity pattern during low-voltage fast activity was confirmed using unit recordings in patients with epilepsy[123]. The enhanced inhibitory activity before a focal seizure might indicate an attempt at seizure prevention[124]. However, others have proposed that enhanced GABA-mediated activity paradoxically precipitates seizures, possibly via increased extracellular potassium levels due to interneuron hyperactivity[125,126]. Indeed, extracellular potassium released during neuronal activity accumulates in the epileptogenic region and enhances neuronal excitability[127]. High extracellular potassium levels lead to neuronal depolarization and eventually cause a selective

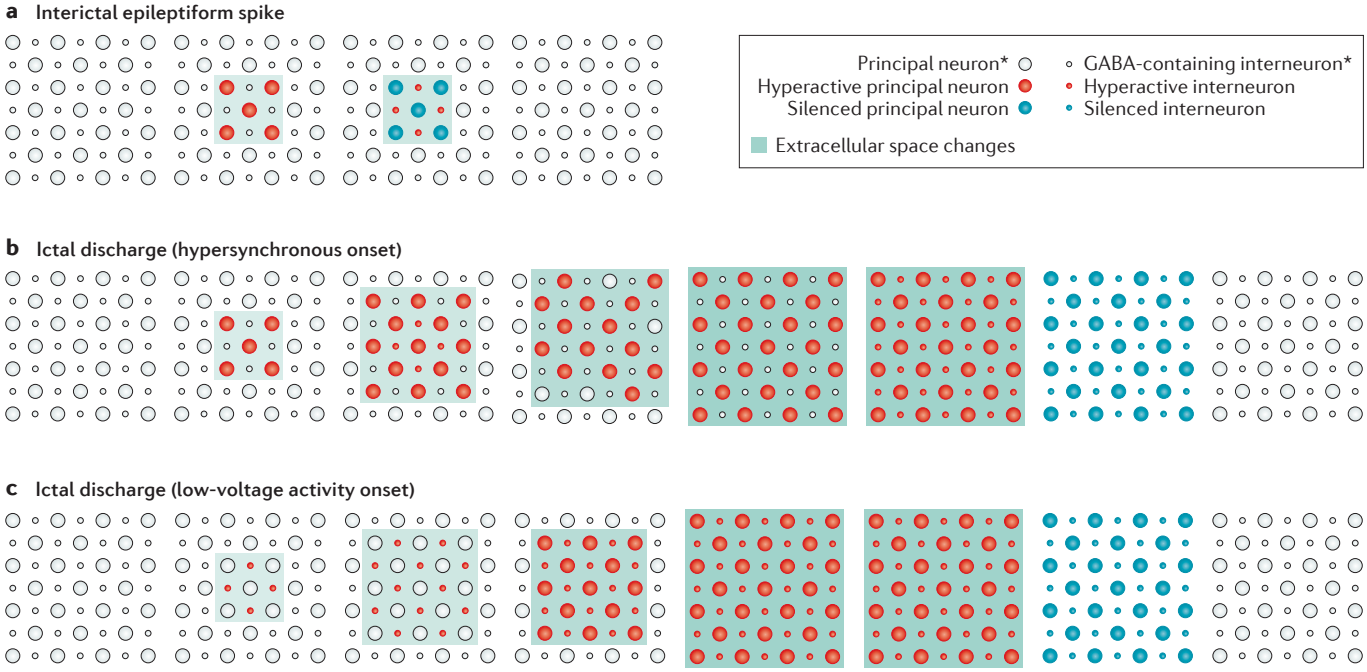

Figure 4 | **Ictogenesis of focal seizures. a** | Schematic sequence of neuronal network activity during ictogenesis of focal seizures. Interictal epileptiform spikes are characterized by transient synchronous hyperexcitability of glutamatergic principal neurons, followed by recurrent interneuron activation. Similar network events on a different spatial scale are responsible for pathological high-frequency oscillations. **b** | A seizure pattern characterized by a prevalent excitatory network activation at onset (that is, hypersynchronous pattern in mesial temporal lobe epilepsy). In this pattern, synchronized principal neurons are active and recruit other principal neurons and interneurons into a larger seizure network. At the same time, extracellular space alterations can enhance neuronal excitability. **c** | Seizure pattern characterized by a prevalent network involvement of γ-aminobutyric acid (GABA)-ergic interneurons at onset (that is, low-voltage fast activity pattern in temporal lobe epilepsy). The initial hyperactivation of inhibitory interneurons and the associated extracellular space modifications recruit synchronous firing of principal neurons. Extracellular changes can contribute either to seizure maintenance and progression (increase in potassium levels, decrease in calcium levels and alterations in pH) or to seizure termination (increase in adenosine and ATP). Darker shading indicates more intense changes in the extracellular space. *Denotes neurons with a physiological background activity.

depolarization block of inhibitory neurons, thereby impairing inhibitory transmission. High potassium levels induce regenerative potentials in principal cells and promote the synchronous firing of these cells, which mediates seizure progression and propagation[128–130]. These are not the only seizure onset mechanisms described. A recent report demonstrated that in the extratemporal olfactory cortex, low-voltage fast activity at seizure onset is sustained by a fast-rising potassium increase due to synaptic hyperactivity of layer I synapses, possibly amplified by further potassium release from unmyelinated fibres located in the same layer[131].

Seizures are self-terminating events that use homeostatic feedback mechanisms induced by the ictal discharge to terminate[132]. Although drastic changes in neuronal membrane properties and energy or neurotransmitter depletion are unlikely during seizures[133], activity-dependent changes in extracellular ions and pH and increased release of adenosine and other inhibitory neuromodulators during the ictal state reduce tissue excitability[132]. During the late phase of a focal seizure, firing of principal cells and GABAergic neurons is enhanced and is synchronized in bursts of spikes. The simultaneous and opposing increased excitation and increased post-burst depression might stop seizures when post-burst inhibition is large enough to prevent the reactivation of excitation[134].

Neuronal synchronization and ictogenesis are also supported by extrasynaptic dysfunction, such as alterations in gap junctions, extracellular ion changes and field effects generated by the synchronous activity of neurons[135,136]. Glia dysfunction can cause seizure-like events *in vitro*[137], and modified astrocyte and BBB functions contribute to seizure generation and spread[38,138,139]. Alterations in astrocytes and microglia functions that regulate neuron–glia interactions (for example, the production and release of inflammatory molecules such as cytokines, danger signals and chemokines[43,44]), ion homeostasis and neuronal metabolism also contribute to seizure generation[33,140]. Finally, the BBB and the periphery can influence seizure activity and onset, and seizures can impair BBB integrity[141]; these might represent underexplored aspects of ictogenesis.

Ictogenesis in patients. The diffusion of long-term (5–10 days) recording with intracranial and intracerebral electrodes during presurgical diagnostic monitoring in patients with drug-resistant focal epilepsy promoted research on human ictogenesis. This research focused mainly on identifying biomarkers of the epileptogenic zone and ictogenesis[142,143], studying cortical processing during cognitive tasks and cortical function, and epileptic network mapping[144]. Computer-assisted algorithms can

detect and predict seizure occurrence during long-term intracranial presurgical recordings. Seizure prediction algorithms have been limited by a lack of reproducibility and within-subject and between-subject variation[145]; larger and more specific data sets are needed to reliably detect pre-seizure states and achieve accurate seizure prediction[146]. Close-loop prediction and/or detection devices have been developed and used in patients, with only detection paradigms showing efficacy at this time[147].

Ictogenesis and intracranial monitoring

The broad use of diagnostic intracranial monitoring in patients with focal epilepsy who are candidates for epilepsy surgery contributed to new data on brain activity during and between seizures. For example, long-term intracranial recordings in patients with the Responsive NeuroStimulation device (see Management) revealed multidien periodicities, most often 20–30 days in duration, that are fairly stable for up to 10 years[148]. These findings changed our view on ictogenesis and refocused basic science studies on human seizure patterns. The analysis of intracranial human recordings has set a new standard to develop animal models that mimic human conditions and will inform the development of novel therapeutic targets and strategies for drug-resistant epilepsy. Neuropathological studies using excised surgical tissue can provide detailed cellular and molecular information on the brain lesions underlying seizures in focal epilepsies[149].

Diagnosis, screening and prevention

The definition of epilepsy, based on combined clinical and epidemiological evidence[1], includes the following: patients with two or more unprovoked or reflex seizures that are >24 hours apart; patients with one unprovoked or reflex seizure who have a ≥60% chance of further seizures over the following 10 years (for example, patients with a known structural lesion such as stroke, severe traumatic brain injury or brain infection[150]); or patients with one or more seizures in the context of a well-defined epilepsy syndrome (for example, childhood epilepsy with centrotemporal spikes).

After one or more paroxysmal events that are suggestive of an epileptic seizure, patients should undergo a thorough clinical assessment and a multistep diagnostic process, including assessment of medical history, physical examination, EEG and neuroimaging. The first step in the diagnosis of epilepsy is to establish whether the event was an epileptic seizure or a seizure mimic[151] (BOX 4). Distinguishing a seizure from a seizure mimic can be challenging, particularly if the event was not witnessed by others or if witness reports are inaccurate. In addition, distinguishing these disorders depends on the context, signs and duration of the event, in addition to post-event features. The second step in diagnosis determines whether the epileptic seizure was unprovoked, reflex or acute symptomatic (BOX 1). Acute symptomatic seizures have a lower risk of subsequent unprovoked seizures than an initial unprovoked seizure[152]. Indeed, the cumulative risk of unprovoked seizures was 18.7% within 10 years after a first acute symptomatic seizure, compared with 64.8% after a first unprovoked seizure after a static brain lesion, in a population-based study in the United States[152]. The third step is to ascertain whether patients presenting with a first unprovoked or reflex seizure have epilepsy. The presenting or 'index seizure' might be preceded by unrecognized seizures, such as isolated epileptic déjà vu. Epileptic déjà vu differs from physiological déjà vu as it lasts longer (typically >5 seconds), is intense and unpleasant and the patient cannot control it. Other types of subtle seizures that might escape recognition include olfactory hallucinations and myoclonic seizures. If previous subtle seizures are identified, then epilepsy can be diagnosed at presentation as the patient has had more than one seizure[153]. Owing to the psychological and social effects of epilepsy, the diagnosis should be based on strong evidence[154]. The fourth step is classifying the seizures into seizure type or types[2], epilepsy type and, where possible, an epilepsy syndrome (Supplementary Box 1). Throughout the diagnostic work-up, there should be strenuous attempts to identify the aetiology of epilepsy[3] as this has important treatment and prognostic implications.

This stepwise diagnostic framework applies to any clinical setting. However, compared with high-income countries, LMICs often face challenges such as limited access to key diagnostic tools, EEG and neuroimaging[155], and in some settings, limited or no access to expert health-care professionals to formulate an accurate epilepsy diagnosis[155].

Medical history

Epilepsy is primarily a clinical diagnosis that relies on a detailed medical history, including a meticulous evaluation of the presenting event and possible precipitating factors. Of patients who have had a seizure and present for medical attention, 23–57% have a history suggestive of prior undiagnosed seizures[156,157]. The previous seizures can include: focal aware seizures with intense déjà vu,

Box 4 | **Differential diagnosis and epilepsy mimics**

Epileptic seizures are often confused with other physiological disorders and psychiatric disorders[151]. Indeed, many conditions can mimic epileptic seizures (see REF. 151 for the full list) and can commonly be misdiagnosed as epilepsy, such as benign paroxysmal positional vertigo, breath-holding attacks, daydreaming, migraine, parasomnias (such as REM sleep behaviour disorder), narcolepsy and/or cataplexy, periodic leg movements during sleep, panic attacks, paroxysmal dyskinesia, psychogenic non-epileptic seizures, sleep apnoea, syncope, tics, transient global amnesia and transient ischaemic attacks[151,276]. Misdiagnosis of one of these conditions as epilepsy can lead to the improper use of anti-seizure medications leading to anti-seizure-drug-associated adverse effects, the loss of driving privileges, social stigma, employment difficulties and failure to diagnose a life-threatening disorder (such as long QT syndrome). By contrast, failure to diagnose epilepsy might lead to a clinician not identifying another condition causing the epilepsy (such as brain tumours or blood vessel malformations) or a seizure that can lead to injury or death.

To further complicate the differential diagnosis, certain disorders commonly coexist. For example, epilepsy often occurs alongside: toxicity due to anti-seizure medications, leading to symptoms that can be mistaken for seizures (which can lead to dose escalation); migraine; anxiety disorders; panic attacks; and cardiac disorders. Indeed, some disorders are often confused with epilepsy and might have clinical and mechanistic overlaps (for example, migraine and depression). Patients with these disorders are more likely to develop epilepsy and vice versa[277]. Both genetic and environmental factors might underlie this relationship[278].

a rising epigastric sensation or gustatory or olfactory hallucinations; brief language difficulties or other features; focal impaired awareness seizures; absence seizures; or myoclonic seizures[153]. In one study of patients presenting with an epileptic seizure, 11.3% had a previous unrecognized seizure and 29.5% had two or more previous seizures[157]. The time frame between the first unrecognized seizure to the presenting seizure can range from weeks to decades[157,158]. Patients presenting with an apparent first seizure should be scrutinized for prior unrecognized seizures, as the presenting seizure — such as a tonic–clonic seizure — is often the first recognized seizure that suggests an epilepsy diagnosis[153].

The patient's experience of the seizure, in addition to eye-witness accounts of the seizure, should be sought as part of the diagnostic work-up. Indeed, witness accounts should be obtained whenever possible and are even more critical for patients who cannot provide a history themselves, such as young children, those with intellectual disability or individuals with peri-ictal amnesia. As many patients have altered awareness or loss of consciousness during seizures, they might deny the event occurred[159]. The widespread use of mobile devices, such as smartphones, provides an excellent opportunity to video events, allows the collection of more-detailed and more-accurate data than witness recollections and can help to identify the seizure type. In addition, videos can be used to differentiate epileptic seizures from non-epileptic events and can be used to identify clinical features (for example, head and eye version) that are not reported by witnesses. In LMICs with limited access to diagnostic tests such as EEG, home videos can be more reliable for identifying seizure signs and classifying the epilepsy type than the description of the events provided by patients' caregivers[160].

Clinicians should ask patients to describe their experiences immediately before, at onset, during and immediately after the event in addition to the context in which the event occurred. Symptoms at the onset that are suggestive of an aura, such as intense déjà vu, a rising epigastric sensation and hallucinations (olfactory, gustatory, visual, auditory or tactile), often indicate a focal seizure and might signal the brain region from which seizures arise. Other features that occur during the seizure and might indicate focal epilepsy include prolonged oral or manual automatisms, unilateral unnatural (dystonic) limb posturing, forced eye and head deviation to one side and asymmetric or unilateral limb jerking. By contrast, generalized seizures are characterized by loss of consciousness at onset.

The patient's medical history should start before birth and include developmental milestones, learning concerns and identify whether the individual has a family history of epilepsy, febrile seizures and other disorders (including intellectual disability, autism spectrum disorder and psychiatric conditions). Other factors that should be taken into account include the age at onset, event duration, triggering factors, diurnal variation, event frequency (including specific patterns of occurrence, such as clustering), the presence of other types of events, the maximum event-free period and injuries related to events.

Physical and neurological examination

Diagnostic work-up should also include a full physical examination, including a neurological examination. Some features, such as lateral tongue biting, can distinguish epileptic seizures from non-epileptic events. Indeed, lateral tongue biting was observed in 22 out of 100 individuals after tonic–clonic seizures but in 0 out of 47 individuals after psychogenic non-epileptic seizures[161]. Syncope might be associated with biting the tip of the tongue rather than the side[162]. Dysmorphic features can suggest genetic syndromes; for example, Down syndrome is associated with infantile spasms, and asymmetry in limb or fingernail size might suggest a perinatal stroke associated with focal seizures[163]. Stigmata of neurocutaneous syndromes include the following: café au lait spots and iris hamartomas in neurofibromatosis; facial port-wine stain in Sturge–Weber syndrome; and facial angiofibromas, periungual fibromas, hypomelanotic macules and shagreen patches in TSC [164]. All patients with epilepsy should be screened for potential cognitive deficits (such as memory problems) and mood or behavioural disturbances (such as depression) and should be considered for more extensive assessment and treatment when indicated. QOL should also be assessed.

EEG

A routine EEG should be performed in patients presenting with an apparent first unprovoked seizure or suspected epilepsy and can help differentiate epileptic seizures from non-epileptic events, classify seizure types and epilepsy syndromes and assist with predicting the risk of seizure recurrence[165,166] (FIG. 5). However, a normal EEG does not exclude an epilepsy diagnosis. Conversely, an abnormal EEG in the absence of a convincing seizure history is not diagnostic of epilepsy. In adults with a first unprovoked seizure, the initial EEG shows epileptiform discharges in an average of 29% of cases (range 8–50%) [166]. The likelihood of detecting epileptiform and non-epileptiform abnormalities is as high as 71% when the EEG is performed within 48 hours of the first seizure[167]. If the initial routine EEG is negative, a sleep-deprived EEG detects epileptiform discharges in an additional 13–35% of cases[168,167]. If diagnostic uncertainty persists, long-term ambulatory EEG or inpatient video-EEG monitoring (when paroxysmal events are fairly frequent) should be considered, when available. The interpretation of long-term EEG data can be aided by automated algorithms for the detection of epileptiform discharges or patients' events[169]. Overall, these tests can improve diagnostic accuracy, particularly if habitual events are recorded, and revise the pre-admission diagnosis in ~60% of patients[170].

Neuroimaging

Neuroimaging should be obtained in all patients with new-onset seizures, except in individuals with genetic (idiopathic) generalized epilepsies, such as childhood absence epilepsy and juvenile myoclonic epilepsy[3,168]. Neuroimaging can aid diagnosis, affect management strategies[171,172] and can be used to identify epileptogenic lesions. Common epileptogenic lesions include

prenatal or perinatal cerebral injury, malformations of cortical development (including focal cortical dysplasia), tumours[171], post-stroke or post-traumatic encephalomalacia, vascular anomalies and hippocampal sclerosis[172]. MRI is the key imaging modality (FIG. 6) and detects an epileptogenic lesion in 14–35% of patients with newly diagnosed unprovoked seizures[172]. CT is often the initial neuroimaging technique used owing to ease of access, but misses many epileptogenic abnormalities. Indeed, 57% of lesions that were identified using MRI were missed using CT in adults and children with a first unprovoked seizure[168]; additional concerns regarding the use of CT include exposure to radiation, particularly in children. Epilepsy-specific MRI protocols and interpretation, and sometimes re-review, of the images by expert neuroradiologists increase the identification of subtle epileptogenic lesions[173]. Advanced post-processing of MRI images can increase the likelihood of detecting subtle abnormalities[174]. Identifying an epileptogenic lesion can inform prognosis and guide management, including the consideration and planning of epilepsy surgery if seizures are not controlled by ASDs. Although the identification of cortical lesions such as tubers or giant cell ependymomas in TSC can influence the selection of anti-epileptic therapy, such as mTOR inhibitors, in general, surgical lesions do not currently influence the choice of ASD therapy[76]. This practice might change as the role of mTOR inhibitors in focal epilepsies is established, as these disorders have a molecular aetiology deriving from pathogenetic variants in the mTOR pathway.

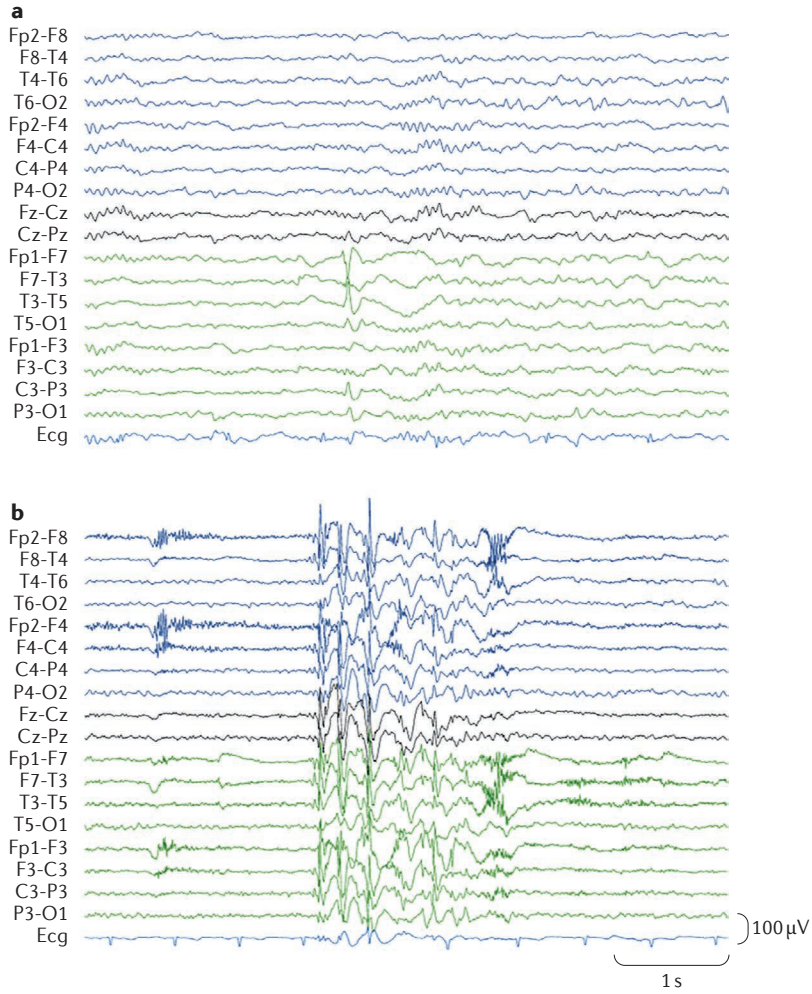

Figure 5 | **Interictal abnormalities detected using EEG. a** | A moderate-amplitude left temporal spike in a patient with non-lesional left temporal lobe epilepsy. **b** | A 2-second burst of bilateral, symmetric, synchronous, high-amplitude, 4 Hz polyspike and wave (a type of spike and wave discharge) in a patient with genetic generalized epilepsy. The abbreviations to the left refer to the location of the electroencephalography (EEG) leads.

Laboratory investigations

After an apparent first unprovoked seizure, several laboratory investigations, such as a complete blood count, assessment of blood glucose levels and electrolyte levels, lumbar puncture and toxicology screening, might be indicated in specific circumstances[165,166]. The awareness of autoimmune aetiologies of epilepsy is increasing[175]. In patients with new-onset and established epilepsies, 11–35% of patients have detectable serum neurological autoantibodies, such as anti-voltage-gated potassium channel antibodies and anti-NMDA receptor antibodies[176,177]. However, whether these antibodies are causative in some patients is unclear. Autoantibody testing is indicated in rare cases in which an autoimmune aetiology is strongly suspected (for example, new onset of frequent seizures, memory impairment and psychiatric symptoms in a previously healthy individual or leucine-rich glioma-inactivated protein 1 autoantibody testing in patients presenting with faciobrachial dystonic seizures and memory deterioration)[178]. Future studies are required to determine whether autoantibody screening should be extended to other clinical presentations.

Genetic testing

Advances in genetic sequencing technologies have dramatically increased the identification of genes and genetic disorders that are associated with epilepsy[179]. Genetic testing is increasingly part of routine patient care; it can lead to a molecular diagnosis and improve clinical outcomes by altering patient management[180]. Several types of genetic testing for epilepsy are available, and the use of these techniques should be decided on the basis of the patient's phenotype, test availability and costs[181,182] (BOX 3; TABLE 2). Genetic testing has the highest yield for developmental and epileptic encephalopathies, which are associated with many causative genes[183]. In these severe epilepsies, the diagnostic yield of chromosomal microarray (also known as a molecular karyotype, single nucleotide polymorphism array or array comparative genome hybridization) is ~5%[184] and is 20–50% for gene panels or whole-exome sequencing[185]. In addition, the aetiology of focal epilepsies can sometimes be identified using genetic testing. For example, in one pilot study, whole-exome sequencing with targeted gene panel analysis detected pathogenetic or likely pathogenetic variants in 12.5% of patients with non-lesional focal epilepsy and a family history of epilepsy or febrile seizure in at least one first-degree or second-degree relative[186]. The detection of epilepsy-causing genetic variants can affect management. For example, the detection of an *SCN1A* mutation in a patient with treatment-resistant

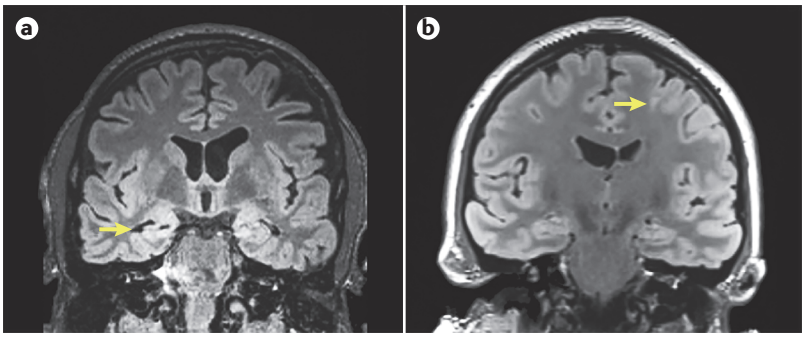

Figure 6 | **Epileptogenic lesions.** MRI has high sensitivity for detecting subtle epileptogenic lesions, such as hippocampal sclerosis and focal cortical dysplasia[166,172]. Identifying focal lesions using MRI improves the likelihood that a patient is a good candidate for epilepsy surgery. **a** | Hippocampal sclerosis (arrow) in a patient with temporal lobe epilepsy detected using coronal fluid-attenuated inversion recovery (FLAIR) imaging. **b** | Focal cortical dysplasia in the left superior frontal gyrus (arrow) in a patient with left frontal lobe epilepsy detected using coronal FLAIR imaging.

TLE led to the discontinuation of longstanding carbamazepine treatment (which can worsen seizures in *SCN1A*-related epilepsies), resulting in the patient obtaining seizure freedom[186].

Management

The care of patients with epilepsy aims to eliminate or reduce seizures, minimize the adverse effects of treatment, improve medical and neuropsychiatric comorbidities and foster an excellent QOL. ASDs are the primary therapy for epilepsy and are symptomatic treatments that reduce seizure occurrence and severity but do not mitigate the course of the disorder[187].

ASDs

ASDs suppress the generation, propagation and severity of epileptic seizures. Early drugs (such as bromide and phenobarbital) had relatively unfavourable efficacy-to-tolerability profiles. Some of the new drugs that have been introduced since the 1990s have advantages over the older ASDs in terms of pharmacokinetics and drug interactions, and some drugs have better tolerability and potentially fewer long-term adverse effects and reduced teratogenicity, although this remains to be proven. However, new drugs have not increased the percentage of seizure-free patients[188,189].

ASDs must be taken between one and four times per day during the epileptic state, which can persist for years, and often for the patient's lifetime. Effective ASD treatment can reduce mortality[190,191]. Inadequate adherence to ASD treatment is common and often leads to seizure recurrence, which is associated with increased death rates, injuries, hospital admissions and costs[191]. Unlike other disorders, such as hypertension, in which an 80% adherence is associated with adequate disease management, a single missed dose of an ASD can lead to a fatal seizure.

ASDs have diverse mechanisms of action, and most drugs have many different cellular effects[192] (TABLE 3), although the full cellular mechanism of many ASDs, particularly valproate, remains uncertain. The mechanisms of action of ASDs correlate poorly with the spectrum of clinical efficacy. The introduction of ASDs with novel mechanisms of action has not reduced the frequency of drug-resistant epilepsy[188,189]. Further, the use of rational polytherapy (that is, attempting to improve efficacy by combining drugs with different mechanisms of action) has minimal supporting evidence. However, the mechanism of action of ASDs can predict adverse effects in patients using ASD polytherapy; for example, patients using two or more ASDs that have a sodium-channel-modulating function have an increased incidence of neurotoxic side effects, such as dizziness, unsteadiness and diplopia[193].

When to commence treatment. Whether to commence treatment with ASDs after the first seizure is controversial, and the decision is based on relative risks, benefits and lifestyle issues. After the first seizure, ~50% of individuals have a second seizure within 3–5 years, with most recurrences within 1 year[194,195]. Several factors can increase the risk of seizure recurrence, including abnormal results on neurological examination, brain imaging or EEG, a family history of epilepsy or a personal history of remote symptomatic seizures[195]. Presenting with multiple seizures within 24 hours or with status epilepticus does not increase the risk of seizure recurrence[194]. In patients with one or more risk factors for seizure recurrence, an ASD is often started after the first seizure. Patient's QOL and safety issues (for example, the patient's occupation, driving status and recreational activities) must be considered in the decision to commence treatment. As previously mentioned, patients with a history of previous seizures have epilepsy, and these patients have a high risk of seizure recurrence without ASDs[158]. Several large trials demonstrated a reduced risk of seizure recurrence in the first 2 years with early ASD treatment but no benefit in long-term seizure control[196,197].

Selecting an ASD. Many different ASDs are available for the treatment of epilepsy. The initial ASD should be individualized on the basis of the epilepsy syndrome and seizure type, the adverse effects profile, the pharmacokinetic profile, potential interactions with other drugs or other medical conditions, the age of the patient, reproductive issues and cost[198]. Randomized controlled trials have demonstrated comparable efficacy of the different ASDs in controlling seizures in patients with focal epilepsy[198]. However, in patients with newly treated idiopathic generalized epilepsy, the time to 12-month seizure remission was significantly longer in patients receiving valproate than in those receiving lamotrigine, and the time to treatment failure (for example, due to inadequate seizure control and/or intolerable adverse effects or the addition of other ASDs) was longer in patients receiving valproate than in those receiving topiramate or lamotrigine[199]. Accordingly, valproate is the first-line therapy in patients with idiopathic generalized epilepsy, except in women of childbearing potential (BOX 5). In children with absence epilepsy, ethosuximide and valproate had equal efficacy at seizure control, and both drugs were superior to lamotrigine. However, ethosuximide was associated with less attentional dysfunction than valproate or lamotrigine[200].

Adverse effects. After starting ASDs, 80% of patients will have adverse effects, and 30–40% of patients will have adverse effects that substantially impair QOL or result in medication cessation or non-adherence[197]. The acute side effects of ASDs are minimized by starting these drugs at low doses and slowly increasing the dose, in addition to reducing the dose if adverse effects develop. The adverse effects and efficacy of these drugs are highly variable between patients; if a patient has troublesome adverse effects with one ASD, another drug might be well tolerated[201].

All ASDs have acute dose-related effects, primarily neurological effects such as sedation, dizziness, unsteadiness, blurred vision, diplopia and tremor, in addition to neurocognitive and psychiatric symptoms. These effects are found across the different ASDs[188,201], but some drugs are better tolerated than others; for example, lamotrigine and levetiracetam are better tolerated that carbamazepine in elderly patients[202]. Psychiatric adverse effects include depression, anxiety, irritability, impaired concentration, mood changes, hyperactivity, and, in rare cases psychosis. Although the newer ASDs are touted as better tolerated than older drugs, psychiatric adverse effects are common with levetiracetam, topiramate, zonisamide, vigabatrin and perampanel[203]. However, lamotrigine, carbamazepine, valproate, gabapentin and pregabalin have mood-stabilizing effects in some patients and less frequently cause behavioural or psychiatric effects[203]. Patients with a past history or a family history of psychiatric disorders or intellectual disability have an increased risk of psychiatric adverse effects with ASD treatment, and patients' mood influences the reporting of adverse effects[204]. Suicide rates are significantly increased in patients with epilepsy compared with the general population[205]. In 2008, the FDA reported an increased risk of suicidal ideation, suicide attempts and completed suicide in randomized controlled add-on trials of ASDs in patients with epilepsy or with other disorders[206]. The increased risk was similar across the 11 ASDs examined and across epilepsy and non-epilepsy indications. However, the FDA alert was widely criticized as other studies and systematic reviews reported no association between ASD treatment and suicidality[207]. However, one case–control study demonstrated that newer ASDs that have a high potential of causing depression were associated with a threefold increased risk of self-harm or suicidal behaviour in patients with epilepsy[208]. In addition, many ASDs have teratogenic effects (BOX 5).

Subacute idiosyncratic adverse effects usually occur weeks or months after starting ASDs, are more common with some drugs and are mostly immune-mediated. The most common effect is an erythematous maculopapular rash, which occurs in 5–10% of patients commenced on carbamazepine, but can also occur with phenytoin, oxcarbazepine, phenobarbitone and lamotrigine. The incidence of lamotrigine erythematous maculopapular rash is reduced by starting patients on low doses and slowly increasing the dose, particularly in patients receiving concomitant valproate. Most ASD-induced rashes are self-limiting if the ASD is stopped, but some can be severe, such as erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, the latter of which can be fatal. In Han Chinese, Hong Kong Chinese or Thai individuals, the *HLA-B*15:02* allele is associated with an increased risk of Stevens–Johnson syndrome with carbamazepine treatment[209]; accordingly, these individuals should be screened for this allele

Table 2 | **Diagnostic genetic testing**

Genetic test	Indication	Genetic defect detected
Currently used		
Chromosomal microarray	• Epilepsies with comorbid intellectual disability, autism spectrum disorder or dysmorphic features • Developmental and epileptic encephalopathies	Copy number variations (such as deletions, duplications and insertion-deletions)
Karyotyping	Suspected ring chromosome 20 syndrome	• Large-scale chromosomal abnormalities • Ring chromosomes (not detected on chromosomal microarray)
Single gene test	• Specific epilepsy syndromes (such as Dravet syndrome or *PCDH19*-associated epilepsy) • Developmental and epileptic encephalopathies	Pathogenetic variants in a single gene (for example, *SCN1A* or *PCDH19*)
Gene panel	• Developmental and epileptic encephalopathies • Progressive myoclonic epilepsies • Focal epilepsies • Other specific epilepsy phenotypes (such as genetic epilepsy with febrile seizures plus)	Pathogenetic variants in up to 500 established epilepsy genes
Whole-exome sequencing	• Individuals in whom chromosomal microarray or gene panels did not identify a molecular diagnosis but in whom a genetic cause is highly suspected • Patients with nonspecific or broad phenotypes in whom a genetic cause is highly suspected	Pathogenetic variants in protein-coding regions of genome
Future relevance		
Whole-genome sequencing	Individuals in whom whole-exome sequencing is negative and a genetic aetiology is likely	Pathogenetic variants in protein-coding and in non-coding regions of the genome

Table 3 | **Putative mechanisms of action and efficacy spectrum of ASDs**

Drug name	Voltage-gated sodium channel blockade	Voltage-gated calcium channel blockade	Enhancement of GABA transmission	Inhibition of glutamate transmission	Other mechanisms[a]	Efficacy spectrum
First-generation ASDs						
Barbiturates	–	?	++	?	+	Most seizure types, excluding absence seizures
Benzodiazepines	–	–	++	–	–	All seizure types but can precipitate tonic seizures, especially after intravenous administration in patients with Lennox–Gastaut syndrome
Carbamazepine	++	+	?	+	+	Focal seizures and generalized tonic–clonic seizures. Can precipitate or aggravate absence seizures and myoclonic seizures
Ethosuximide	–	++	–	–	?	Absence seizures
Phenytoin	++	?	?	?	+	Focal seizures and generalized tonic–clonic seizures. Can precipitate or aggravate absence seizures and myoclonic seizures
Valproic acid	?	+	+	+	++	All seizure types
Second-generation ASDs						
Brivaracetam	+	–	?	–	++	Focal seizures
Eslicarbazepine acetate	++	–	–	–	–	Focal seizures. Can precipitate or aggravate absence seizures and myoclonic seizures
Everolimus	?	?	?	?	++	Seizures associated only with tuberous sclerosis
Felbamate	++	+	+	++	+	Focal seizures and drop attacks associated with Lennox–Gastaut syndrome
Gabapentin	–	++	?	–	?	Focal seizures. Can precipitate or aggravate myoclonic seizures
Lacosamide	++	–	–	–	+	Focal seizures
Lamotrigine	++	++	+	++	+	Most seizure types. Can precipitate or aggravate myoclonic seizures. Efficacy is best reported in focal seizures, generalized tonic–clonic seizures, absence seizures and drop attacks associated with Lennox–Gastaut syndrome
Levetiracetam	–	+	?	?	++	Most seizure types. Efficacy against tonic and atonic seizures has not been documented. Efficacy is best reported in focal seizures, generalized tonic–clonic seizures and myoclonic seizures
Oxcarbazepine	++	+	?	+	+	Focal seizures and generalized tonic–clonic seizures. Can precipitate or aggravate absence seizures and myoclonic seizures
Perampanel	–	–	–	++	–	Focal seizures and generalized tonic–clonic seizures
Pregabalin	–	++	–	–	–	Focal seizure types. Can precipitate or aggravate myoclonic seizures
Rufinamide	++	–	–	?	–	Focal seizures and drop attacks associated with Lennox–Gastaut syndrome
Stiripentol	–	–	++	–	–	Only indicated for use in combination with clobazam and valproic acid for tonic–clonic seizures associated with Dravet syndrome
Tiagabine	–	–	++	–	–	Focal seizure types. Can precipitate or aggravate absence seizures and myoclonic seizures
Topiramate	++	+	++	++	+	Most seizure types. Efficacy against absence seizures has not been reported. Efficacy is best reported in focal seizures, generalized tonic–clonic seizures and drop attacks associated with Lennox–Gastaut syndrome
Vigabatrin	–	–	++	–	–	Focal seizure types and infantile spasms. Can precipitate or aggravate myoclonic seizures
Zonisamide	++	++	+	?	+	Most seizure types. The efficacy in most types of generalized seizure is poorly documented. Efficacy is best reported in focal seizures

Table 3 (cont.) | **Putative mechanisms of action and efficacy spectrum of ASDs**

Drug name	Voltage-gated sodium channel blockade	Voltage-gated calcium channel blockade	Enhancement of GABA transmission	Inhibition of glutamate transmission	Other mechanisms[a]	Efficacy spectrum
Selected in-development ASDs (phase III studies)						
Cannabidiol	–	?	?	?	+	Motor seizures associated with Dravet syndrome and drop attacks associated with Lennox–Gastaut syndrome
Cenobamate	++	?	?	?	?	Focal seizures
Ganaxolone	?	?	++	?	?	Focal seizures and infantile spasms

+ indicates a secondary mechanism action; ++ indicates primary mechanism of action; – indicates that this mechanism has not been described; ? indicates controversy. ASDs, anti-seizure drugs; GABA, γ-aminobutyric acid. [a]Include synaptic vesicle 2A modulation (levetiracetam and brivaracetam), mechanistic target of rapamycin (mTOR) pathway inhibition (everolimus) and carbonic anhydrase inhibition (zonisamide and topiramate). Adapted with permission from (REF. 289), Elsevier.

before carbamazepine is prescribed. Uncommon subacute hypersensitivity reactions to ASDs include systemic hypersensitivity syndrome, which causes malaise, fever, lymphadenitis, arthralgia, eosinophilia, hepatitis, acute haemorrhagic pancreatitis, blood dyscrasias and hyponatraemia.

Long-term adverse effects of ASDs that manifest after years of treatment can affect metabolic, neurological, haematological, dermatological, immunological and other systems. Patients treated with ASDs have a twofold to threefold increased risk of bone fractures[210], which likely reflects a combined effect of the ASDs on bone health and fragility and balance rather than a direct effect of seizures[210]. In addition, increased body weight and fat are common in patients using valproate, carbamazepine, gabapentin, pregabalin, vigabatrin and perampanel and can lead to serious health consequences associated with obesity, increased abdominal fat, metabolic syndrome and increased cardiovascular disease risk[211]. However, some ASDs (such as topiramate, zonisamide, felbamate, stiripentol and rufinamide) can cause weight loss, and some have no effect on weight.

Drug-resistant epilepsy

In patients with epilepsy who commence ASD treatment, ~50% will achieve seizure control after the first drug, a further 13% will achieve seizure control after the second drug but <4% will achieve seizure control after the failure of two ASDs. 36% of patients have uncontrolled seizures no matter how many ASDs are trialled, using monotherapy or combination drugs[212]. The outcomes of newly treated epilepsy and chances of drug resistance remain largely unchanged from earlier studies, despite the availability of multiple new ASDs[189].

Drug-resistant epilepsy is defined as the failure of adequate trials of two or more tolerated, appropriately chosen and appropriately used ASD regimens (whether administered as monotherapies or in combination) to achieve seizure freedom[213,214]. This condition is more common in patients who have multiple (more than five) seizures before treatment, a longer duration of epilepsy before treatment, an abnormal MRI, epileptiform discharges detected using EEG, focal seizures, a remote symptomatic aetiology and neurocognitive deficits or symptomatology[215]. Drug-resistant epilepsy is associated with an increased risk of injury and death, greater medication burden and adverse effects, increased psychiatric and neurocognitive comorbidities, socioeconomic disadvantage and reduced QOL[214].

Treatment options for drug-resistant epilepsy include trying other ASDs, epilepsy surgery, neurostimulation devices and dietary therapies. Of these, epilepsy surgery offers the greatest chance of achieving long-term seizure control, but only a minority of patients are good candidates. Patients with seizures that persist after two appropriate ASDs should be referred to an epilepsy centre to confirm the diagnosis and evaluate whether they are suitable for epilepsy surgery[214]. This evaluation ideally includes long-term inpatient video-EEG monitoring and is extremely useful, as up to 30% of patients with drug-resistant epilepsy have non-epileptic seizures, and many patients undergo therapeutic changes on the basis of video-EEG findings[170]. In addition, pseudo-drug resistance, due to the wrong diagnosis, the incorrect drug for the epilepsy syndrome, inadequate dosing, medication non-adherence or lifestyle factors (such as sleep deprivation, drug or alcohol abuse), should be considered in patients with uncontrolled seizures[214].

Resective surgery. Resective surgery can lead to long-term seizure control in some patients, with some eventually ceasing ASD therapy. The most frequently performed epilepsy surgery is an anterior temporal lobectomy in patients with drug-resistant mesial TLE. Indeed, this surgery is superior to continued medication for long-term seizure freedom in patients with drug-resistant mesial TLE[4].

An MRI lesion (for example, mesial temporal sclerosis, focal cortical dysplasia or a neocortical mass) that can be completely resected is the strongest prognostic factor for long-term postoperative seizure control in patients with drug-resistant epilepsy[216]. Indeed, ≥80% of patients with these lesions remain seizure free for ≥12 months after surgery[216,217]. In addition, after epilepsy surgery, seizure-free patients have improved QOL (including patient satisfaction, employment and independence[4]) and reduced medication burden[216], injury, hospitalization, death rates[218], psychiatric morbidity[219] and direct costs of care[220]. However, epilepsy surgery

can lead to memory or language deficits for dominant-hemisphere resections, mood disturbances, headaches, infections and strokes in a minority of patients.

Patients lacking a localized MRI lesion, particularly if the epileptogenic zone is outside the temporal lobe, have poorer outcomes for seizure control after epilepsy surgery than patients with a localized MRI lesion[216]. New imaging techniques such as PET, subtraction (ictal–interictal) single-photon emission CT and magnetoencephalography can be used to identify the epileptogenic zone in some patients with non-lesional drug-resistant focal epilepsy and improve seizure freedom rates with epilepsy surgery[221]. However, most patients with non-lesional epilepsy who have an epileptogenic zone outside the temporal lobe require implantation with intracranial EEG electrodes to localize the epileptogenic zone before resective epilepsy surgery, but these studies increase the risk of morbidity and mortality[222]. Functional imaging, such as functional MRI, can identify cortical regions involved in specific cognitive and sensorimotor functions. These studies guide safe resection to avoid loss of critical functions during epilepsy surgery.

Neurostimulation. The implantation of a neurostimulation device is an alternative therapy for patients with drug-resistant epilepsy who are not suitable for resective surgery. The vagus nerve stimulator (VNS) was the first approved neurostimulation device for epilepsy. Randomized controlled trials demonstrated a 24–31% reduction in seizure frequency over 3 months in patients receiving a therapeutic high VNS treatment paradigm compared with a reduction of 6–15% in patients who received a low, subtherapeutic stimulation[223]. However, open-labelled, uncontrolled studies with longer follow-up periods have demonstrated a ≥50% reduction in seizure frequency in at least 50% of patients, with the maximum efficacy achieved after only 2 years in some patients. VNS is also associated with improved QOL, fewer hospitalizations due to status epilepticus and reduced mortality[223,224]. More recently, a randomized, double-blind, controlled trial demonstrated a reduction in seizure frequency with neurostimulation using electrodes implanted into the anterior nucleus of the thalamus[225] and closed-loop stimulation with the Responsive NeuroStimulation device, which uses surface and/or depth electrodes, compared with sham stimulations[226]. The responder rate was similar across the three devices, as was evidence of improved QOL and reduced mortality during the open-label follow-up study, but no study directly compared them. Few patients are rendered seizure free with neurostimulation; thus, these devices are not alternatives to epilepsy surgery in patients with well-defined seizure foci that can be safely removed. Devices to record and treat epilepsy are rapidly developing, with ongoing efforts to predict seizures or enhance memory or other cognitive functions[227].

Dietary therapies. Although the ketogenic diet has been used since the 1920s, mainly in children with severe epilepsies, the past two decades have seen a resurgence in the use of dietary therapies for epilepsy, including broader dietary options (such as the modified Atkins diet or the low-glycaemic diet) and use in different patient populations (such as adults)[228,229]. More than 50% of patients treated with a ketogenic diet have a >50% seizure reduction, one-third have >90% seizure reduction and some patients are rendered seizure free[229]. The ketogenic diet is the treatment of choice for some metabolic disorders that can cause epilepsy (such as GLUT1 deficiency and pyruvate dehydrogenase deficiency) and might be effective for refractory status epilepticus[230]. The mean percentage reduction in seizure frequency relative to baseline in a randomized controlled trial in children with epilepsy was lower in the ketogenic diet versus control group (62% versus 137%), with 38% versus 6% having ≥50% seizure reduction[231]. The ketogenic diet has a similar efficacy in patients with drug-resistant focal and generalized epilepsy. However, the ketogenic diet has poor tolerability and adverse effects (such as constipation, vomiting, lack of energy and hunger) that limit adherence in adults, who adhere better to the modified Atkins diet[232]. Long-term complications of dietary therapies include nutritional deficiency, growth impairment in children, abnormal lipid profile, osteopenia and kidney stones[233]. Rigorous clinical trials in adults are required before the effectiveness and long-term safety of these dietary therapies is established.

Box 5 | **Treatment of women of childbearing potential**

Anti-seizure drugs (ASDs) can cause harmful effects to the fetus in pregnant women. Indeed, birth defects occur in 6–8% of pregnancies in women with epilepsy who use ASDs during the first trimester compared with ~3% in the general population or in women with epilepsy who do not use ASDs[279]. Most first-generation ASDs, and some second-generation ASDs, are classified as pregnancy category D (proven human teratogens), whereas the other newer ASDs are classified as pregnancy category C (not enough supporting evidence ensure these drugs are safe in pregnancy, but some data from animal studies or the pharmacology of the drugs raise concern). However, despite teratogenicity, many women need to continue to take these drugs during pregnancy owing to the potential dangerous effects of uncontrolled seizures on both maternal or fetal health.

International pregnancy registers provide invaluable information on the relative teratogenic risks of ASDs and doses[280]. Valproate and phenobarbitone are particularly teratogenic as monotherapy or polytherapy. Indeed, valproate-induced teratogenicity is dose-dependent and is associated with higher risk of spina bifida and hypospadias[281,282]. Consequently, the International League Against Epilepsies and the American Academy of Neurology guidelines recommend avoiding the administration of valproate to women of childbearing potential unless other ASDs cannot control the seizures, in which case the dose should be kept as low as possible. Indeed, some patients with idiopathic generalized epilepsy can control their seizures only with valproate. The increased teratogenic effects associated with polytherapy versus monotherapy remain controversial[283,284]; combining low-dose valproate with lamotrigine or levetiracetam in patients with idiopathic generalized epilepsy has less risk of teratogenicity than high-dose valproate monotherapy. Topiramate polytherapy is associated with an increased risk of teratogenicity compared with monotherapy[285].

The use of ASDs during pregnancy increases the risk of neurocognitive problems in offspring during infancy and childhood, including autism spectrum disorder[286,287]. This risk is greatest with valproate therapy. Although teratogenic effects are largely limited to the use of ASDs during the first trimester (during organogenesis), effects on brain development can occur with ASD use during any stage of pregnancy. In addition, brain development continues following birth; thus, exposure to ASDs in breast milk could affect postnatal development. However, children of mothers using ASDs, including valproate, who were breastfed have IQ outcomes at least as high as children who were not breastfed[288].

Quality of life

Doctors traditionally view patients with epilepsy using the main outcome measures of seizure control and medication adverse effects. However, practitioners and patients have different concerns; for example, patients are more concerned about memory deficits than practitioners[234]. In adult and paediatric epilepsy, QOL measures reveal important patient-reported outcomes of treatments[235,236], and abbreviated QOL measures can be incorporated into routine care. Although clinicians assume that seizure frequency predicts QOL in patients with epilepsy, only seizure freedom — not a reduced seizure frequency — is associated with higher health-related QOL[237]. Indeed, in patients with treatment-resistant epilepsy, seizure frequency is a poor predictor of QOL[237,238]. Other key determinants of QOL (such as the presence of mood disturbances, adverse effects of ASDs, reduced sexual function, stress and sleep disturbances) are often unrecognized and untreated by neurologists.

Comorbidities

Mental health. Depressive symptoms and other symptoms of low mental health are the strongest independent predictor of QOL in patients with epilepsy[238], and subclinical depressive symptoms can severely affect QOL[239]. This finding is particularly important as depression is found in ~30% of patients with epilepsy[240] and in ≥50% of patients with treatment-resistant epilepsy[238]. Depression is a major cause of mortality and morbidity in patients with epilepsy and is associated with reduced adherence to medication, seizure control, sleep, employment and sexual function, which further impair QOL[238,241]. Other psychiatric disorders, such as anxiety and psychosis, can also severely impair QOL in patients with epilepsy[242]. Attempted and completed suicides are more than threefold higher in patients with epilepsy than in the general population[13,243]. In addition, patients with epilepsy and comorbid psychiatric disorders are 13-fold more likely to die owing to suicide, vehicular accidents, falls, drowning and drug poisoning (mainly psychiatric and opioid medications) than patients without psychiatric illness[243].

Individuals with epilepsy also report higher levels of stress than the general population, and stress can provoke seizures, either directly or indirectly (by impairing sleep or medication adherence)[244]. In addition, stressful events can increase EEG epileptiform activity[245], blood-oxygen-level-dependent functional MRI reactivity, heart rate and cortisol levels[246]. Anxiety, stress and depression correlate with increased seizure frequency in longitudinal studies; depression was associated with the highest seizure frequency[247]. These findings emphasize the importance of diagnosing and treating depression and other psychiatric disorders in patients with epilepsy.

Sexual function. Sexual dysfunction is common in patients with epilepsy and is associated with reduced QOL[248]. These problems can result from pharmacological or illness-specific mechanisms[249]. Many ASDs are metabolized in the hepatic cytochrome P450 system, which induces enzymes that increase the metabolism of sex hormones and the synthesis of sex hormone-binding globulin — both of which can diminish sexual function. However, in many cases, the involvement of areas that regulate emotions and drive-related behaviours by the underlying cause of epilepsy or seizures can also impair libido or sexual function.

Management of comorbidities. Therapeutic interventions targeting behavioural changes and self-management skills can reduce stress and depressive symptoms in patients with epilepsy[250]. Self-management is a critical part of patient-centred care and can focus on medication adherence, lifestyle changes (for example, improved sleep hygiene and avoidance of excess alcohol) and/or depressive symptoms. For example, project UPLIFT is an 8-week self-management intervention that combines cognitive behavioural therapy, mindfulness and relaxation techniques and can improve depressive symptoms and life satisfaction in patients with epilepsy[250]. In addition, one prospective, randomized study demonstrated an improvement in mood with supervised exercise in adults with epilepsy, compared with those with no intervention[234]. Indeed, increased physical activity is associated with lower levels of depression in patients with epilepsy[251], and exercise might also reduce seizure activity[252]. Furthermore, low cardiovascular fitness in early life is associated with an increased risk of epilepsy[253]. Finally, for individuals with sexual dysfunction, the potential role of ASDs should be considered and referral for psychological or sex therapy can be considered. Use of medications for erectile dysfunction (for example, phosphodiesterase inhibitors) or low libido (for example, flibanserin) is safe for patients with epilepsy.

Outlook

The future for people with epilepsy grows brighter with time. Major inroads are being made into areas such as imaging, genetics and neurophysiology. Conversely, some issues are still to be addressed, such as the debilitating, life-changing impact of the unpredictable nature of seizures (for example, how to prevent the cascade of events that leads to a seizure occurring at a particular time). Seizure prediction tools are emerging but are yet to become sophisticated enough to assist most patients with epilepsy[227]. Why some epilepsies are drug-resistant, and how this can be changed also require further study. Inflammation is emerging as a critical player in epilepsy and suggests that greater understanding of the role of anti-inflammatory therapies has the potential to alleviate the impact of this disorder.

Improvements in imaging

Novel imaging techniques are delineating epilepsy networks, including white matter tracts as well as regions of abnormal formation and connectivity, inflammation and metabolism. Functional imaging techniques can identify patterns of seizure onset and spread and inform the safety and efficacy of surgical approaches. Ongoing studies in animal models and patients are investigating whether neuroimaging techniques can predict neurological outcomes and the development of epilepsy after

acute brain injuries. In addition, an increasing list of potential prognostic blood-based biomarkers are being validated in both animal models and patients, and these biomarkers might also predict the therapeutic response in patients.

Epilepsy genetics

Two decades ago, genetic factors were rarely considered in the aetiology of epilepsy. However, the discovery of many epilepsy genes has radically altered this view, with exciting new insights into epilepsy genetics emerging on a weekly basis. (BOX 3).

High levels of mosaicism (in which there are two populations of cells that are genetically distinct) are found in normal brains and are relevant when searching for genetic causes of epilepsy as they might cause the patient's epilepsy[254,255]. Low levels (<20%) of a mosaic mutation are not detected by conventional Sanger sequencing, and a pathogenetic variant is likely to be missed if present at a low level of mosaicism unless special molecular studies are conducted. In some instances, the mutation might be somatic and limited to brain tissue and not detectable in blood or other tissues. Mosaicism limited to the gonads is a critical issue for reproductive testing as it considerably increases the recurrence risk of a family. Often, parental mosaicism is not recognized until the family has two children with epilepsy, highlighting the need for earlier and more rigorous approaches to parental testing, such as high-depth coverage of their child's mutation to detect low levels of mosaicism[256].

Other potential novel genetic mechanisms include epigenetic abnormalities, in which changes in DNA methylation affect gene transcription. In addition, little is known about environmental effects on gene expression, which remains a critical target for future research as the concordance of epilepsy in identical twins varies from 40% (for focal epilepsies) to 85% (for generalized epilepsies), supporting a role for gene–environment interactions.

For patients with developmental and epileptic encephalopathies, detecting mutations (pathogenetic variants) in 30–50% of patients has greatly changed diagnosis and management[183]. In addition, identifying the molecular basis of focal epilepsy informs clinical management; for example, patients with *DEPDC5* mutations should undergo high-resolution MRI to detect a subtle focal cortical dysplasia that might allow epilepsy surgery[257]. Understanding pathogenetic variants that cause epilepsy offers new therapeutic opportunities. For example, upregulating the expression of the normal gene in patients with haploinsufficiency disorders is an enticing possibility; loss of function is usual in Dravet syndrome, which is due to an *SCN1A* mutation in >80% cases. Accordingly, global initiatives to solve the genetics of the common epilepsies are underway. These disorders might result from complex inheritance, involving multiple genes and possible environmental factors. The large number of patients required for these studies, together with the requisite technology and bioinformatics expertise, are now possible, and exciting results are expected in the next few years.

Targeted 'precision' therapies

As knowledge regarding the aetiologies of epilepsy and the pathophysiology of seizures increases, targeted therapies are becoming a reality (Supplementary Table 1). Critical insights from gene discovery in epilepsy are driving this change. In addition, increased knowledge of the molecular alterations that lead to permanent changes in neuronal network structure and function after epileptogenic brain insults has opened new avenues for developing new mechanism-based treatments. Further studies into the mechanisms of epileptogenesis induced by genetic mutations and comparison with mechanisms induced by acquired brain insults are warranted. Notably, drugs targeting epileptogenic mechanisms used for other clinical indications are being considered for use in epilepsy[87,258,259].

Precision medicine holds great promise for patients with epilepsy. Small targeted studies using a novel or repurposed compound are now being employed to reverse the dysfunction caused by a genetic mutation. For example, *in vitro,* quinidine (a potassium channel blocker) counters gain-of-function mutations in *KCNT1* (encoding a potassium channel subunit)-associated epilepsies[260,261]. Patients with *KCNT1* mutations develop either of two severe epilepsy syndromes: epilepsy of infancy with migrating focal seizures or severe autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)[261,262]. Case reports suggest that quinidine significantly reduces seizure frequency and improves development in children with *KCNT1* mutations[263,264]; however, quinidine treatment was ineffective in a double-blind, randomized, placebo-controlled trial in patients with severe ADNFLE[265]. These contradictory findings might be due to the specific mutation type or the location of the mutation within the gene, the cell type expressing the mutant protein, modifier genes or other factors such as clinical trial design. Rigorous therapeutic trials of precision medicines are needed to ensure safety and efficacy. However, developing specific drugs for each gene may be unrealistic. More 'generic' approaches might emerge as we identify the convergence of overlapping pathways. For instance, patients with genetic abnormalities in the mTOR pathway leading to focal epilepsy might benefit from mTOR inhibitors. A well-designed trial has already demonstrated efficacy for everolimus in reducing seizure frequency in patients with TSC[76].

Prevention

Cerebral insults, such as severe traumatic brain injury, brain tumours and stroke, or CNS infections are associated with a substantially increased risk of epilepsy[266]. Conceptually, these insults initiate an epileptogenic process that culminates in an unprovoked seizure after weeks, months or years. This latent period is a potential opportunity to intervene and stop this process, thereby preventing the development of epilepsy. However, although many ASDs have been investigated for their ability to prevent the occurrence of unprovoked seizures after a major cerebral insult, none have prevented epilepsy[267]. Identifying biomarkers of epileptogenesis and pathogenetic mechanisms in animal models could allow the development of targeted preventive therapies[44,266].

1. Fisher, R. S. et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* **55**, 475–482 (2014).
2. Fisher, R. S. et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* **58**, 522–530 (2017).
3. Scheffer, I. E. et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* **58**, 512–521 (2017).
4. Wiebe, S., Blume, W. T., Girvin, J. P. & Eliasziw, M. A. Randomized, controlled trial of surgery for temporal-lobe epilepsy. *N. Engl. J. Med.* **345**, 311–318 (2001).
5. Hauser, W. A. & Beghi, E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* **49**, 8–12 (2008).
6. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1545–1602 (2016).
7. Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W. & Newton, C. R. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia* **51**, 883–890 (2010).
8. Fiest, K. M. et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology* **88**, 296–303 (2017).
9. Singh, A. & Trevick, S. The epidemiology of global epilepsy. *Neurol. Clin.* **34**, 837–847 (2016).
10. Bharucha, N. E., Bharucha, E. P., Bharucha, A. E., Bhise, A. V. & Schoenberg, B. S. Prevalence of epilepsy in the Parsi community of Bombay. *Epilepsia* **29**, 111–115 (1988).
11. Devinsky, O., Spruill, T., Thurman, D. & Friedman, D. Recognizing and preventing epilepsy-related mortality. *Neurology* **86**, 779–786 (2016).
12. Levira, F. et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* **58**, 6–16 (2016).
13. Thurman, D. J. et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* **58**, 17–26 (2017).
14. Twele, F., Töllner, K., Brandt, C. & Löscher, W. Significant effects of sex, strain, and anesthesia in the intrahippocampal kainate mouse model of mesial temporal lobe epilepsy. *Epilepsy Behav.* **55**, 47–56 (2016).
15. Noebels, J. Pathway-driven discovery of epilepsy genes. *Nat. Neurosci.* **18**, 344–350 (2015).
This article reviews discoveries in epilepsy genetics from *de novo* exome variants in patients, targeted mutations in model systems and *in vivo* and *ex vivo* systems to better understand epilepsy and its treatment.
16. Kitz, S. et al. Feline temporal lobe epilepsy: review of the experimental literature. *J. Vet. Intern. Med.* **31**, 633–640 (2017).
17. Patterson, E. E. Canine epilepsy: an underutilized model. *ILAR J.* **55**, 182–186 (2014).
18. Terrone, G., Salamone, A. & Vezzani, A. Inflammation and epilepsy: preclinical findings and potential clinical translation. *Curr. Pharm. Des.* **23**, 5569–5576 (2018).
19. Dudek, F. E. & Staley, K. J. The time course of acquired epilepsy: implications for therapeutic intervention to suppress epileptogenesis. *Neurosci. Lett.* **497**, 240–246 (2011).
20. Pitkänen, A., Lukasiuk, K., Dudek, F. E. & Staley, K. J. Epileptogenesis. *Cold Spring Harb. Perspect. Med.* **5**, a022822 (2015).
21. Ravizza, T. et al. WONOEP appraisal: Biomarkers of epilepsy-associated comorbidities. *Epilepsia* **58**, 331–342 (2017).
22. Varvel, N. H., Jiang, J. & Dingledine, R. Candidate drug targets for prevention or modification of epilepsy. *Annu. Rev. Pharmacol. Toxicol.* **55**, 229–247 (2015).
23. Buckmaster, P. S. Mossy fiber sprouting in the dentate gyrus. *Jasper's Basic Mechanisms of the Epilepsies* https://www.ncbi.nlm.nih.gov/books/NBK98174/ (2012).
24. Sloviter, R. S., Zappone, C. A., Harvey, B. D. & Frotscher, M. Kainic acid-induced recurrent mossy fiber innervation of dentate gyrus inhibitory interneurons: possible anatomical substrate of granule cell hyper-inhibition in chronically epileptic rats. *J. Comp. Neurol.* **494**, 944–960 (2006).
25. Heck, N., Garwood, J., Loeffler, J.-P., Larmet, Y. & Faissner, A. Differential upregulation of extracellular matrix molecules associated with the appearance of granule cell dispersion and mossy fiber sprouting during epileptogenesis in a murine model of temporal lobe epilepsy. *Neuroscience* **129**, 309–324 (2004).
26. Hester, M. S. & Danzer, S. C. Hippocampal granule cell pathology in epilepsy — a possible structural basis for comorbidities of epilepsy? *Epilepsy Behav.* **38**, 105–116 (2014).
27. Parent, J. M. & Kron, M. M. Neurogenesis and epilepsy. *Jasper's Basic Mechanisms of the Epilepsies* https://www.ncbi.nlm.nih.gov/books/NBK98198/ (2012).
28. Ribak, C. E. et al. Seizure-induced formation of basal dendrites on granule cells of the rodent dentate gyrus. *Jasper's Basic Mechanisms of the Epilepsies* https://www.ncbi.nlm.nih.gov/books/NBK98199/ (2012).
29. Orcinha, C. et al. Seizure-induced motility of differentiated dentate granule cells is prevented by the central Reelin fragment. *Front. Cell. Neurosci.* **10**, 183 (2016).
30. Cho, K.-O. et al. Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. *Nat. Commun.* **6**, 6606 (2015).
31. Zeng, L.-H., Rensing, N. R. & Wong, M. The mammalian target of rapamycin signaling pathway mediates epileptogenesis in a model of temporal lobe epilepsy. *J. Neurosci.* **29**, 6964–6972 (2009).
32. Buckmaster, P. S. & Lew, F. H. Rapamycin suppresses mossy fiber sprouting but not seizure frequency in a mouse model of temporal lobe epilepsy. *J. Neurosci.* **31**, 2337–2347 (2011).
33. Devinsky, O., Vezzani, A., Najjar, S., De Lanerolle, N. C. & Rogawski, M. A. Glia and epilepsy: excitability and inflammation. *Trends Neurosci.* **36**, 174–184 (2013).
34. Ortinski, P. I. et al. Selective induction of astrocytic gliosis generates deficits in neuronal inhibition. *Nat. Neurosci.* **13**, 584–591 (2010).
35. Robel, S. et al. Reactive astrogliosis causes the development of spontaneous seizures. *J. Neurosci.* **35**, 3330–3345 (2015).
36. Boison, D. Adenosinergic signaling in epilepsy. *Neuropharmacology* **104**, 131–139 (2016).
This study examines the role of the purinergic system in epilepsy, exemplifying how one of many relevant signalling pathways influences epileptogenesis, comorbidities and epigenetics.
37. Oberheim, N. A. et al. Loss of astrocytic domain organization in the epileptic brain. *J. Neurosci.* **28**, 3264–3276 (2008).
38. Steinhäuser, C., Grunnet, M. & Carmignoto, G. Crucial role of astrocytes in temporal lobe epilepsy. *Neuroscience* **323**, 157–169 (2016).
39. Eyo, U. B., Murugan, M. & Wu, L.-J. Microglia-neuron communication in epilepsy. *Glia* **65**, 5–18 (2017).
40. Dubé, C. M. et al. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J. Neurosci.* **30**, 7484–7494 (2010).
41. Tegelberg, S., Kopra, O., Joensuu, T., Cooper, J. D. & Lehesjoki, A.-E. Early microglial activation precedes neuronal loss in the brain of the Cstb$^{-/-}$ mouse model of progressive myoclonus epilepsy, EPM1. *J. Neuropathol. Exp. Neurol.* **71**, 40–53 (2012).
42. Okuneva, O. et al. Abnormal microglial activation in the Cstb($^{-/-}$) mouse, a model for progressive myoclonus epilepsy, EPM1. *Glia* **63**, 400–411 (2015).
43. Vezzani, A., Maroso, M., Balosso, S., Sanchez, M.-A. & Bartfai, T. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain Behav. Immun.* **25**, 1281–1289 (2011).
44. Aronica, E. et al. Neuroinflammatory targets and treatments for epilepsy validated in experimental models. *Epilepsia* **58** (Suppl. 3), 27–38 (2017).
This paper describes a rapidly evolving area in clinical and basic epilepsy science — the role of neuroinflammation in pathogenesis and treatment.
45. Russmann, V. et al. Minocycline fails to exert antiepileptogenic effects in a rat status epilepticus model. *Eur. J. Pharmacol.* **771**, 29–39 (2016).
46. Wang, N. et al. Minocycline inhibits brain inflammation and attenuates spontaneous recurrent seizures following pilocarpine-induced status epilepticus. *Neuroscience* **287**, 144–156 (2015).
47. Benson, M. J., Manzanero, S. & Borges, K. Complex alterations in microglial M1/M2 markers during the development of epilepsy in two mouse models. *Epilepsia* **56**, 895–905 (2015).
48. Librizzi, L., Noè, F., Vezzani, A., de Curtis, M. & Ravizza, T. Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. *Ann. Neurol.* **72**, 82–90 (2012).
49. Xu, Y. et al. Regulation of endothelial intracellular adenosine via adenosine kinase epigenetically modulates vascular inflammation. *Nat. Commun.* **8**, 943 (2017).
50. Fabene, P. F. et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. *Nat. Med.* **14**, 1377–1383 (2008).
51. Bar-Klein, G. et al. Imaging blood-brain barrier dysfunction as a biomarker for epileptogenesis. *Brain* **140**, 1692–1705 (2017).
52. Weissberg, I. et al. Albumin induces excitatory synaptogenesis through astrocytic TGF-β/ALK5 signaling in a model of acquired epilepsy following blood-brain barrier dysfunction. *Neurobiol. Dis.* **78**, 115–125 (2015).
53. Nehlig, A. What is animal experimentation telling us about new drug treatments of status epilepticus? *Epilepsia* **48** (Suppl. 8), 78–81 (2007).
54. Dingledine, R. et al. Transcriptional profile of hippocampal dentate granule cells in four rat epilepsy models. *Sci. Data* **4**, 170061 (2017).
55. van Loo, K. M. J. et al. Zinc regulates a key transcriptional pathway for epileptogenesis via metal-regulatory transcription factor 1. *Nat. Commun.* **6**, 8688 (2015).
56. Dezsi, G. et al. Ethosuximide reduces epileptogenesis and behavioral comorbidity in the GAERS model of genetic generalized epilepsy. *Epilepsia* **54**, 635–643 (2013).
57. Russo, E. et al. Effects of early long-term treatment with antiepileptic drugs on development of seizures and depressive-like behavior in a rat genetic absence epilepsy model. *Epilepsia* **52**, 1341–1350 (2011).
58. Catterall, W. A. Sodium channel mutations and epilepsy. *Jasper's Basic Mechanisms of the Epilepsies* https://www.ncbi.nlm.nih.gov/books/NBK98185/ (2012).
59. Benarroch, E. E. HCN channels: function and clinical implications. *Neurology* **80**, 304–310 (2013).
60. McClelland, S. et al. The transcription factor NRSF contributes to epileptogenesis by selective repression of a subset of target genes. *eLife* **3**, e01267 (2014).
61. Grabenstatter, H. L. et al. The effect of STAT3 inhibition on status epilepticus and subsequent spontaneous seizures in the pilocarpine model of acquired epilepsy. *Neurobiol. Dis.* **62**, 73–85 (2014).
62. Henshall, D. C. et al. MicroRNAs in epilepsy: pathophysiology and clinical utility. *Lancet Neurol.* **15**, 1368–1376 (2016).
63. Henshall, D. C. & Kobow, K. Epigenetics and epilepsy. *Cold Spring Harb. Perspect. Med.* **5**, a022731 (2015).
64. Machnes, Z. M. et al. DNA methylation mediates persistent epileptiform activity *in vitro* and *in vivo*. *PLoS ONE* **8**, e76299 (2013).
65. Williams-Karnesky, R. L. et al. Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. *J. Clin. Invest.* **123**, 3552–3563 (2013).
66. Göttlicher, M. et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J.* **20**, 6969–6978 (2001).
67. Iori, V. et al. Blockade of the IL-1R1/TLR4 pathway mediates disease-modification therapeutic effects in a model of acquired epilepsy. *Neurobiol. Dis.* **99**, 12–23 (2017).
68. Reschke, C. R. et al. Potent anti-seizure effects of locked nucleic acid antagomirs targeting miR-134 in multiple mouse and rat models of epilepsy. *Mol. Ther. Nucleic Acids* **6**, 45–56 (2017).
69. McNamara, J. O. & Scharfman, H. E. Temporal lobe epilepsy and the BDNF receptor, TrkB. *Jasper's Basic Mechanisms of the Epilepsies* https://www.ncbi.nlm.nih.gov/books/NBK98186/ (2012).
70. Scharfman, H. E. & Brooks-Kayal, A. R. Is plasticity of GABAergic mechanisms relevant to epileptogenesis? *Adv. Exp. Med. Biol.* **813**, 133–150 (2014).
71. Ostendorf, A. P. & Wong, M. mTOR inhibition in epilepsy: rationale and clinical perspectives. *CNS Drugs* **29**, 91–99 (2015).
72. Guo, D., Zeng, L., Brody, D. L. & Wong, M. Rapamycin attenuates the development of posttraumatic epilepsy in a mouse model of traumatic brain injury. *PLoS ONE* **8**, e64078 (2013).

73. Way, S. W. et al. The differential effects of prenatal and/or postnatal rapamycin on neurodevelopmental defects and cognition in a neuroglial mouse model of tuberous sclerosis complex. *Hum. Mol. Genet.* **21**, 3226–3236 (2012).
74. Hartman, A. L., Santos, P., Dolce, A. & Hardwick, J. M. The mTOR inhibitor rapamycin has limited acute anticonvulsant effects in mice. *PLoS ONE* **7**, e45156 (2012).
75. Raffo, E., Coppola, A., Ono, T., Briggs, S. W. & Galanopoulou, A. S. A pulse rapamycin therapy for infantile spasms and associated cognitive decline. *Neurobiol. Dis.* **43**, 322–329 (2011).
76. French, J. A. et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet* **388**, 2153–2163 (2016).
77. Boison, D. Adenosine kinase: exploitation for therapeutic gain. *Pharmacol. Rev.* **65**, 906–943 (2013).
78. Li, T., Quan Lan, J., Fredholm, B. B., Simon, R. P. & Boison, D. Adenosine dysfunction in astrogliosis: cause for seizure generation? *Neuron Glia Biol.* **3**, 353–366 (2007).
79. Masino, S. A. et al. A ketogenic diet suppresses seizures in mice through adenosine A_1 receptors. *J. Clin. Invest.* **121**, 2679–2683 (2011).
80. Cacheaux, L. P. et al. Transcriptome profiling reveals TGF-beta signaling involvement in epileptogenesis. *J. Neurosci.* **29**, 8927–8935 (2009).
81. Kim, S. Y. et al. TGFβ signaling is associated with changes in inflammatory gene expression and perineuronal net degradation around inhibitory neurons following various neurological insults. *Sci. Rep.* **7**, 7711 (2017).
82. Xanthos, D. N. & Sandkühler, J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nat. Rev. Neurosci.* **15**, 43–53 (2014).
83. Rowley, S. & Patel, M. Mitochondrial involvement and oxidative stress in temporal lobe epilepsy. *Free Radic. Biol. Med.* **62**, 121–131 (2013).
84. Pauletti, A. et al. Targeting oxidative stress improves disease outcomes in a rat model of acquired epilepsy. *Brain* **140**, 1885–1899 (2017).
85. Vezzani, A. & Viviani, B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology* **96**, 70–82 (2015).
86. Mazarati, A. M., Lewis, M. L. & Pittman, Q. J. Neurobehavioral comorbidities of epilepsy: Role of inflammation. *Epilepsia* **58** (Suppl. 3), 48–56 (2017).
87. Kenney-Jung, D. L. et al. Febrile infection-related epilepsy syndrome treated with anakinra. *Ann. Neurol.* **80**, 939–945 (2016).
88. Ben-Menachem, E., Kyllerman, M. & Marklund, S. Superoxide dismutase and glutathione peroxidase function in progressive myoclonus epilepsies. *Epilepsy Res.* **40**, 33–39 (2000).
89. Kovac, S. & Walker, M. C. Neuropeptides in epilepsy. *Neuropeptides* **47**, 467–475 (2013).
90. Biagini, G. et al. Neurosteroids and epileptogenesis. *J. Neuroendocrinol.* **25**, 980–990 (2013).
91. Gao, F. et al. Fingolimod (FTY720) inhibits neuroinflammation and attenuates spontaneous convulsions in lithium-pilocarpine induced status epilepticus in rat model. *Pharmacol. Biochem. Behav.* **103**, 187–196 (2012).
92. Hong, S. et al. The PPARγ agonist rosiglitazone prevents cognitive impairment by inhibiting astrocyte activation and oxidative stress following pilocarpine-induced status epilepticus. *Neurol. Sci.* **33**, 559–566 (2012).
93. Mantoan Ritter, L. et al. WONOEP appraisal: optogenetic tools to suppress seizures and explore the mechanisms of epileptogenesis. *Epilepsia* **55**, 1693–1702 (2014).
94. Pitkänen, A., Buckmaster, P. S., Galanopoulou, A. S. & Moshé, S. L. *Models of Seizures and Epilepsy* 2nd edn (Academic Press, 2017).
95. Raimondo, J. V. et al. Methodological standards for *in vitro* models of epilepsy and epileptic seizures. A TASK1-WG4 report of the AES/ILAE Translational Task Force of the ILAE. *Epilepsia* **58**, 40–52 (2017).
96. Avoli, M. A brief history on the oscillating roles of thalamus and cortex in absence seizures. *Epilepsia* **53**, 779–789 (2012).
97. Crunelli, V. & Leresche, N. Childhood absence epilepsy: genes, channels, neurons and networks. *Nat. Rev. Neurosci.* **3**, 371–382 (2002).
98. Tsakiridou, E., Bertollini, L., de Curtis, M., Avanzini, G. & Pape, H. C. Selective increase in T-type calcium conductance of reticular thalamic neurons in a rat model of absence epilepsy. *J. Neurosci.* **15**, 3110–3117 (1995).
99. Cope, D. W. et al. Enhanced tonic GABAA inhibition in typical absence epilepsy. *Nat. Med.* **15**, 1392–1398 (2009).
100. Maheshwari, A. & Noebels, J. L. Monogenic models of absence epilepsy: windows into the complex balance between inhibition and excitation in thalamocortical microcircuits. *Prog. Brain Res.* **213**, 223–252 (2014).
101. Onat, F. Y., van Luijtelaar, G., Nehlig, A. & Snead, O. C. The involvement of limbic structures in typical and atypical absence epilepsy. *Epilepsy Res.* **103**, 111–123 (2013).
102. Sitnikova, E. & van Luijtelaar, G. Electroencephalographic characterization of spike-wave discharges in cortex and thalamus in WAG/Rij rats. *Epilepsia* **48**, 2296–2311 (2007).
103. Depaulis, A., David, O. & Charpier, S. The genetic absence epilepsy rat from Strasbourg as a model to decipher the neuronal and network mechanisms of generalized idiopathic epilepsies. *J. Neurosci. Methods* **260**, 159–174 (2016).
104. Bai, X. et al. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. *J. Neurosci.* **30**, 5884–5893 (2010).
105. Perucca, P., Dubeau, F. & Gotman, J. Intracranial electroencephalographic seizure-onset patterns: effect of underlying pathology. *Brain* **137**, 183–196 (2014).
106. Ayala, G. F., Matsumoto, H. & Gumnit, R. J. Excitability changes and inhibitory mechanisms in neocortical neurons during seizures. *J. Neurophysiol.* **33**, 73–85 (1970).
107. Johnston, D. & Brown, T. H. Giant synaptic potential hypothesis for epileptiform activity. *Science* **211**, 294–297 (1981).
108. de Curtis, M. & Avanzini, G. Interictal spikes in focal epileptogenesis. *Prog. Neurobiol.* **63**, 541–567 (2001).
109. Toprani, S. & Durand, D. M. Long-lasting hyperpolarization underlies seizure reduction by low frequency deep brain electrical stimulation. *J. Physiol.* **591**, 5765–5790 (2013).
110. Koubeissi, M. Z., Kahriman, E., Syed, T. U., Miller, J. & Durand, D. M. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. *Ann. Neurol.* **74**, 223–231 (2013).
111. Keller, C. J. et al. Heterogeneous neuronal firing patterns during interictal epileptiform discharges in the human cortex. *Brain* **133**, 1668–1681 (2010).
112. Avoli, M. & de Curtis, M. GABAergic synchronization in the limbic system and its role in the generation of epileptiform activity. *Prog. Neurobiol.* **95**, 104–132 (2011).
113. Chauvière, L. et al. Changes in interictal spike features precede the onset of temporal lobe epilepsy. *Ann. Neurol.* **71**, 805–814 (2012).
114. Salami, P. et al. Dynamics of interictal spikes and high-frequency oscillations during epileptogenesis in temporal lobe epilepsy. *Neurobiol. Dis.* **67**, 97–106 (2014).
115. Zijlmans, M. et al. High-frequency oscillations as a new biomarker in epilepsy. *Ann. Neurol.* **71**, 169–178 (2012).
116. Engel, J. & da Silva, F. L. High-frequency oscillations — where we are and where we need to go. *Prog. Neurobiol.* **98**, 316–318 (2012).
117. Bragin, A., Benassi, S. K., Kheiri, F. & Engel, J. Further evidence that pathologic high-frequency oscillations are bursts of population spikes derived from recordings of identified cells in dentate gyrus. *Epilepsia* **52**, 45–52 (2011).
118. Ogren, J. A. et al. Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. *Ann. Neurol.* **66**, 783–791 (2009).
119. Avoli, M., de Curtis, M. & Köhling, R. Does interictal synchronization influence ictogenesis? *Neuropharmacology* **69**, 37–44 (2013).
120. Bragin, A., Azizyan, A., Almajano, J., Wilson, C. L. & Engel, J. Analysis of chronic seizure onsets after intrahippocampal kainic acid injection in freely moving rats. *Epilepsia* **46**, 1592–1598 (2005).
121. de Curtis, M. & Avoli, M. GABAergic networks jump-start focal seizures. *Epilepsia* **57**, 679–687 (2016).
122. Grasse, D. W., Karunakaran, S. & Moxon, K. A. Neuronal synchrony and the transition to spontaneous seizures. *Exp. Neurol.* **248**, 72–84 (2013).
123. Truccolo, W. et al. Single-neuron dynamics in human focal epilepsy. *Nat. Neurosci.* **14**, 635–641 (2011).
124. Schevon, C. A. et al. Evidence of an inhibitory restraint of seizure activity in humans. *Nat. Commun.* **3**, 1060 (2012).
125. Avoli, M. et al. Specific imbalance of excitatory/inhibitory signaling establishes seizure onset pattern in temporal lobe epilepsy. *J. Neurophysiol.* **115**, 3229–3237 (2016).
126. Librizzi, L. et al. Interneuronal network activity at the onset of seizure-like events in entorhinal cortex slices. *J. Neurosci.* **37**, 10398–10407 (2017).
127. Traynelis, S. F. & Dingledine, R. Potassium-induced spontaneous electrographic seizures in the rat hippocampal slice. *J. Neurophysiol.* **59**, 259–276 (1988).
128. Sessolo, M. et al. Parvalbumin-positive inhibitory interneurons oppose propagation but favor generation of focal epileptiform activity. *J. Neurosci.* **35**, 9544–9557 (2015).
129. Ziburkus, J., Cressman, J. R., Barreto, E. & Schiff, S. J. Interneuron and pyramidal cell interplay during *in vitro* seizure-like events. *J. Neurophysiol.* **95**, 3948–3954 (2006).
130. Trombin, F., Gnatkovsky, V. & de Curtis, M. Changes in action potential features during focal seizure discharges in the entorhinal cortex of the *in vitro* isolated guinea pig brain. *J. Neurophysiol.* **106**, 1411–1423 (2011).
131. Uva, L. et al. A novel focal seizure pattern generated in superficial layers of the olfactory cortex. *J. Neurosci.* **37**, 3544–3554 (2017).
132. Lado, F. A. & Moshé, S. L. How do seizures stop? *Epilepsia* **49**, 1651–1664 (2008).
133. Farrell, J. S. et al. Postictal hypoperfusion/hypoxia provides the foundation for a unified theory of seizure-induced brain abnormalities and behavioral dysfunction. *Epilepsia* **58**, 1493–1501 (2017).
134. Boido, D., Gnatkovsky, V., Uva, L., Francione, S. & de Curtis, M. Simultaneous enhancement of excitation and postburst inhibition at the end of focal seizures. *Ann. Neurol.* **76**, 826–836 (2014).
135. Jefferys, J. G. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiol. Rev.* **75**, 689–723 (1995).
136. Carlen, P. L. Curious and contradictory roles of glial connexins and pannexins in epilepsy. *Brain Res.* **1487**, 54–60 (2012).
137. Tian, G.-F. et al. An astrocytic basis of epilepsy. *Nat. Med.* **11**, 973–981 (2005).
138. Vezzani, A., French, J., Bartfai, T. & Baram, T. Z. The role of inflammation in epilepsy. *Nat. Rev. Neurol.* **7**, 31–40 (2011).
139. Marchi, N., Granata, T., Ghosh, C. & Janigro, D. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. *Epilepsia* **53**, 1877–1886 (2012).
140. Crunelli, V., Carmignoto, G. & Steinhäuser, C. Novel astrocyte targets: new avenues for the therapeutic treatment of epilepsy. *Neuroscientist* **21**, 62–83 (2015).
141. Heinemann, U., Kaufer, D. & Friedman, A. Blood-brain barrier dysfunction, TGFβ signaling, and astrocyte dysfunction in epilepsy. *Glia* **60**, 1251–1257 (2012).
142. David, O. et al. Imaging the seizure onset zone with stereo-electroencephalography. *Brain* **134**, 2898–2911 (2011).
143. Gnatkovsky, V. et al. Biomarkers of epileptogenic zone defined by quantified stereo-EEG analysis. *Epilepsia* **55**, 296–305 (2014).
144. Bartolomei, F. et al. Defining epileptogenic networks: contribution of SEEG and signal analysis. *Epilepsia* **58**, 1131–1147 (2017).
145. Mormann, F., Andrzejak, R. G., Elger, C. E. & Lehnertz, K. Seizure prediction: the long and winding road. *Brain* **130**, 314–333 (2007).
146. Freestone, D. R. et al. Seizure prediction: science fiction or soon to become reality? *Curr. Neurol. Neurosci. Rep.* **15**, 73 (2015).
147. Sun, F. T. & Morrell, M. J. Closed-loop neurostimulation: the clinical experience. *Neurotherapeutics* **11**, 553–563 (2014).
148. Baud, M. O. et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat. Commun.* **9**, 88 (2018).
149. Blumcke, I. et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N. Engl. J. Med.* **377**, 1648–1656 (2017).
150. Hauser, W. A., Rich, S. S., Lee, J. R.-J., Annegers, J. F. & Anderson, V. E. Risk of recurrent seizures after two unprovoked seizures. *N. Engl. J. Med.* **338**, 429–434 (1998).

151. [No authors listed.] Epilepsy imitators. *International League Against Epilepsy* https://www.epilepsydiagnosis.org/epilepsy-imitators.html. (2018).
152. Hesdorffer, D. C., Benn, E. K. T., Cascino, G. D. & Hauser, W. A. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia* **50**, 1102–1108 (2009).
153. Pohlmann-Eden, B. The first seizure and its management in adults and children. *BMJ* **332**, 339–342 (2006).
154. Hermann, B. & Jacoby, A. The psychosocial impact of epilepsy in adults. *Epilepsy Behav.* **15**, S11–S16 (2009).
155. Katchanov, J. & Birbeck, G. L. Epilepsy care guidelines for low- and middle- income countries: from WHO mental health GAP to national programs. *BMC Med.* **10**, 107 (2012).
156. Hamiwka, L. D., Singh, N., Niosi, J. & Wirrell, E. C. Diagnostic inaccuracy in children referred with 'first seizure': role for a first seizure clinic. *Epilepsia* **48**, 1062–1066 (2007).
157. Firkin, A. L. et al. Mind the gap: Multiple events and lengthy delays before presentation with a 'first seizure'. *Epilepsia* **56**, 1534–1541 (2015).
158. Jallon, P., Loiseau, P. & Loiseau, J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. *Epilepsia* **42**, 464–475 (2001).
159. Blumenfeld, H. Impaired consciousness in epilepsy. *Lancet Neurol.* **11**, 814–826 (2012).
This is an insightful paper on one of the most disabling symptoms of seizures and how seizures can inform us about brain function.
160. Dash, D. et al. Can home video facilitate diagnosis of epilepsy type in a developing country? *Epilepsy Res.* **125**, 19–23 (2016).
161. Brigo, F. et al. Tongue biting in epileptic seizures and psychogenic events. *Epilepsy Behav.* **25**, 251–255 (2012).
162. Benbadis, S. R. Value of tongue biting in the diagnosis of seizures. *Arch. Intern. Med.* **155**, 2346–2349 (1995).
163. Ahmed, S. N. & Spencer, S. S. An approach to the evaluation of a patient for seizures and epilepsy. *WMJ* **103**, 49–55 (2004).
164. Klar, N., Cohen, B. & Lin, D. D. M. Neurocutaneous syndromes. *Handb. Clin. Neurol.* **135**, 565–589 (2016).
165. Hirtz, D. et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. *Neurology* **55**, 616–623 (2000).
166. Krumholz, A. et al. Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* **69**, 1996–2007 (2007).
167. Schreiner, A. & Pohlmann-Eden, B. Value of the early electroencephalogram after a first unprovoked seizure. *Clin. Electroencephalogr.* **34**, 140–144 (2003).
168. King, M. A. et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* **352**, 1007–1011 (1998).
169. Ramgopal, S. et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy Behav.* **37**, 291–307 (2014).
170. Ghougassian, D. F., d'Souza, W., Cook, M. J. & O'Brien, T. J. Evaluating the utility of inpatient video-EEG monitoring. *Epilepsia* **45**, 928–932 (2004).
171. Berg, A. T. et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain* **132**, 2785–2797 (2009).
172. Hakami, T. et al. MRI-identified pathology in adults with new-onset seizures. *Neurology* **81**, 920–927 (2013).
173. McBride, M. C. et al. Failure of standard magnetic resonance imaging in patients with refractory temporal lobe epilepsy. *Arch. Neurol.* **55**, 346–348 (1998).
174. Bernasconi, A., Bernasconi, N., Bernhardt, B. C. & Schrader, D. Advances in MRI for 'cryptogenic' epilepsies. *Nat. Rev. Neurol.* **7**, 99–108 (2011).
175. Bien, C. G. & Holtkamp, M. 'Autoimmune epilepsy': encephalitis with autoantibodies for epileptologists. *Epilepsy Curr.* **17**, 134–141 (2017).
This article is a focused review of the emerging field of autoantibody-induced epilepsy.
176. Brenner, T. et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. *Epilepsia* **54**, 1028–1035 (2013).
177. Dubey, D. et al. Neurological autoantibody prevalence in epilepsy of unknown etiology. *JAMA Neurol.* **74**, 397 (2017).
178. Irani, S. R. et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann. Neurol.* **69**, 892–900 (2011).
179. Thomas, R. H. & Berkovic, S. F. The hidden genetics of epilepsy — a clinically important new paradigm. *Nat. Rev. Neurol.* **10**, 283–292 (2014).
180. Scheffer, I. Epilepsy genetics revolutionizes clinical practice. *Neuropediatrics* **45**, 70–74 (2014).
181. Mefford, H. C. Clinical genetic testing in epilepsy. *Epilepsy Curr.* **15**, 197–201 (2015).
182. Poduri, A. When should genetic testing be performed in epilepsy patients? *Epilepsy Curr.* **17**, 16–22 (2017).
183. McTague, A., Howell, K. B., Cross, J. H., Kurian, M. A. & Scheffer, I. E. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol.* **15**, 304–316 (2016).
184. Mefford, H. C. et al. Rare copy number variants are an important cause of epileptic encephalopathies. *Ann. Neurol.* **70**, 974–985 (2011).
185. Mercimek-Mahmutoglu, S. et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. *Epilepsia* **56**, 707–716 (2015).
186. Perucca, P. et al. Real-world utility of whole exome sequencing with targeted gene analysis for focal epilepsy. *Epilepsy Res.* **131**, 1–8 (2017).
187. Pitkänen, A. Therapeutic approaches to epileptogenesis — hope on the horizon. *Epilepsia* **51**, 2–17 (2010).
188. Löscher, W. & Schmidt, D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia* **52**, 657–678 (2011).
189. Chen, Z., Brodie, M. J., Liew, D. & Kwan, P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs. *JAMA Neurol.* **75**, 279 (2018).
190. Ryvlin, P., Cucherat, M. & Rheims, S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol.* **10**, 961–968 (2011).
191. Faught, E., Duh, M. S., Weiner, J. R., Guerin, A. & Cunnington, M. C. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology* **71**, 1572–1578 (2008).
192. Rogawski, M. A. & Löscher, W. The neurobiology of antiepileptic drugs. *Nat. Rev. Neurosci.* **5**, 553–564 (2004).
193. Novy, J., Patsalos, P. N., Sander, J. W. & Sisodiya, S. M. Lacosamide neurotoxicity associated with concomitant use of sodium channel-blocking antiepileptic drugs: a pharmacodynamic interaction? *Epilepsy Behav.* **20**, 20–23 (2011).
194. Kho, L. K., Lawn, N. D., Dunne, J. W. & Linto, J. First seizure presentation: do multiple seizures within 24 hours predict recurrence? *Neurology* **67**, 1047–1049 (2006).
195. Wiebe, S., Tellez-Zenteno, J. F. & Shapiro, M. An evidence-based approach to the first seizure. *Epilepsia* **49**, 50–57 (2008).
196. Camfield, P., Camfield, C., Smith, S., Dooley, J. & Smith, E. Long-term outcome is unchanged by antiepileptic drug treatment after a first seizure: a 15-year follow-up from a randomized trial in childhood. *Epilepsia* **43**, 662–663 (2002).
197. Marson, A. et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* **365**, 2007–2013 (2005).
198. Glauser, T. et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* **54**, 551–563 (2013).
This article is an evidence-based review of anti-seizure medication efficacies.
199. Marson, A. G. et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* **369**, 1016–1026 (2007).
200. Glauser, T. A. et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N. Engl. J. Med.* **362**, 790–799 (2010).
201. Hakami, T. et al. Substitution monotherapy with levetiracetam versus older antiepileptic drugs. *Arch. Neurol.* **69**, 1563 (2012).
202. Werhahn, K. J. et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* **56**, 450–459 (2015).
203. Ettinger, A. B. Psychotropic effects of antiepileptic drugs. *Neurology* **67**, 1916–1925 (2006).
204. Perucca, P. et al. Adverse antiepileptic drug effects in new-onset seizures: a case-control study. *Neurology* **76**, 273–279 (2011).
205. Christensen, J., Vestergaard, M., Mortensen, P. B., Sidenius, P. & Agerbo, E. Epilepsy and risk of suicide: a population-based case–control study. *Lancet Neurol.* **6**, 693–698 (2007).
206. Busko, M. FDA advisory members agree antiepileptics pose suicidality risk, nix need for black-box warning. *Medscape* http://www.medscape.com/viewarticle/577432 (2008).
207. Hesdorffer, D. C. & Kanner, A. M. The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? *Epilepsia* **50**, 978–986 (2009).
208. Andersohn, F., Schade, R., Willich, S. N. & Garbe, E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. *Neurology* **75**, 335–340 (2010).
209. Chen, P. et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N. Engl. J. Med.* **364**, 1126–1133 (2011).
210. Shiek Ahmad, B. et al. Falls and fractures in patients chronically treated with antiepileptic drugs. *Neurology* **79**, 145–151 (2012).
211. Chukwu, J., Delanty, N., Webb, D. & Cavalleri, G. L. Weight change, genetics and antiepileptic drugs. *Expert Rev. Clin. Pharmacol.* **7**, 43–51 (2013).
212. Kwan, P. & Brodie, M. J. Early identification of refractory epilepsy. *N. Engl. J. Med.* **342**, 314–319 (2000).
213. Kwan, P. et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **51**, 1069–1077 (2009).
214. Kwan, P., Schachter, S. C. & Brodie, M. J. Drug-resistant epilepsy. *N. Engl. J. Med.* **365**, 919–926 (2011).
215. Sillanpää, M. & Schmidt, D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. *Brain* **132**, 989–998 (2009).
216. Tellez-Zenteno, J. F., Dhar, R. & Wiebe, S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* **128**, 1188–1198 (2005).
217. Lowe, A. J. et al. Epilepsy surgery for pathologically proven hippocampal sclerosis provides long-term seizure control and improved quality of life. *Epilepsia* **45**, 237–242 (2004).
218. Bell, G. S. et al. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? *J. Neurol. Neurosurg. Psychiatry* **81**, 716–718 (2010).
219. Devinsky, O. et al. Changes in depression and anxiety after resective surgery for epilepsy. *Neurology* **65**, 1744–1749 (2005).
220. Schiltz, N. K., Kaiboriboon, K., Koroukian, S. M., Singer, M. E. & Love, T. E. Long-term reduction of health care costs and utilization after epilepsy surgery. *Epilepsia* **57**, 316–324 (2016).
221. O'Brien, T. J. et al. The cost-effective use of 18F-FDG PET in the presurgical evaluation of medically refractory focal epilepsy. *J. Nucl. Med.* **49**, 931–937 (2008).
222. Liubinas, S. V., Cassidy, D., Roten, A., Kaye, A. H. & O'Brien, T. J. Tailored cortical resection following image guided subdural grid implantation for medically refractory epilepsy. *J. Clin. Neurosci.* **16**, 1398–1408 (2009).
223. Milby, A. H., Halpern, C. H. & Baltuch, G. H. Vagus nerve stimulation in the treatment of refractory epilepsy. *Neurotherapeutics* **6**, 228–237 (2009).
224. Ryvlin, P. et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia* **59**, 562–572 (2018).
225. Fisher, R. et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* **51**, 899–908 (2010).
226. Morrell, M. J. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* **77**, 1295–1304 (2011).
227. Cook, M. J. et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol.* **12**, 563–571 (2013).
228. Cervenka, M. C., Henry, B. J., Felton, E. A., Patton, K. & Kossoff, E. H. Establishing an adult epilepsy diet center: experience, efficacy and challenges. *Epilepsy Behav.* **58**, 61–68 (2016).
229. Lefevre, F. & Aronson, N. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. *Pediatrics* **105**, e46–e46 (2000).

230. Cervenka, M. C. et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. *Neurology* **88**, 938–943 (2017).
231. Neal, E. G. et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol.* **7**, 500–506 (2008).
232. Kossoff, E. H. & Dorward, J. L. The modified Atkins diet. *Epilepsia* **49**, 37–41 (2008).
233. Kang, H. C., Chung, D. E., Kim, D. W. & Kim, H. D. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia* **45**, 1116–1123 (2004).
234. McAuley, J. W. et al. Comparing patients' and practitioners' views on epilepsy concerns: a call to address memory concerns. *Epilepsy Behav.* **19**, 580–583 (2010).
235. Devinsky, O. et al. Development of the quality of life in epilepsy inventory. *Epilepsia* **36**, 1089–1104 (1995).
236. Cowan, J. & Baker, G. A. A review of subjective impact measures for use with children and adolescents with epilepsy. *Qual. Life Res.* **13**, 1435–1443 (2004).
237. Choi, H. et al. Seizure frequency and patient-centered outcome assessment in epilepsy. *Epilepsia* **55**, 1205–1212 (2014).
238. Boylan, L. S. et al. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* **62**, 258–261 (2004).
239. Kanner, A. M., Barry, J. J., Gilliam, F., Hermann, B. & Meador, K. J. Anxiety disorders, subsyndromic depressive episodes, and major depressive episodes: do they differ on their impact on the quality of life of patients with epilepsy? *Epilepsia* **51**, 1152–1158 (2010).
240. Fiest, K. M. et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology* **80**, 590–599 (2013).
241. DiMatteo, M. R., Lepper, H. S. & Croghan, T. W. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch. Intern. Med.* **160**, 2101–2107 (2000).
242. Hamid, H. et al. Mood, anxiety, and incomplete seizure control affect quality of life after epilepsy surgery. *Neurology* **82**, 887–894 (2014).
243. Fazel, S., Wolf, A., Långström, N., Newton, C. R. & Lichtenstein, P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* **382**, 1646–1654 (2013).
244. McKee, H. R. & Privitera, M. D. Stress as a seizure precipitant: Identification, associated factors, and treatment options. *Seizure* **44**, 21–26 (2017).
245. Galtrey, C. M., Mula, M. & Cock, H. R. Stress and epilepsy: fact or fiction, and what can we do about it? *Pract. Neurol.* **16**, 270–278 (2016).
246. Allendorfer, J. B. & Szaflarski, J. P. Contributions of fMRI towards our understanding of the response to psychosocial stress in epilepsy and psychogenic nonepileptic seizures. *Epilepsy Behav.* **35**, 19–25 (2014).
247. Thapar, A., Kerr, M. & Harold, G. Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures. *Epilepsy Behav.* **14**, 134–140 (2009).
248. Atif, M., Sarwar, M. R. & Scahill, S. The relationship between epilepsy and sexual dysfunction: a review of the literature. *Springerplus* **5**, 2070 (2016).
249. Yang, Y. & Wang, X. Sexual dysfunction related to antiepileptic drugs in patients with epilepsy. *Expert Opin. Drug Saf.* **15**, 31–42 (2016).
250. Thompson, N. J. et al. Expanding the efficacy of Project UPLIFT: distance delivery of mindfulness-based depression prevention to people with epilepsy. *J. Consult. Clin. Psychol.* **83**, 304–313 (2015).
251. Arida, R. M., de Almeida, A.-C. G., Cavalheiro, E. A. & Scorza, F. A. Experimental and clinical findings from physical exercise as complementary therapy for epilepsy. *Epilepsy Behav.* **26**, 273–278 (2013).
252. de Lima, C. et al. Physiological and electroencephalographic responses to acute exhaustive physical exercise in people with juvenile myoclonic epilepsy. *Epilepsy Behav.* **22**, 718–722 (2011).
253. Nyberg, J. et al. Cardiovascular fitness and later risk of epilepsy: a Swedish population-based cohort study. *Neurology* **81**, 1051–1057 (2013).
254. Depienne, C. et al. Mechanisms for variable expressivity of inherited SCN1A mutations causing Dravet syndrome. *J. Med. Genet.* **47**, 404–410 (2010).
255. Lodato, M. A. et al. Somatic mutation in single human neurons tracks developmental and transcriptional history. *Science* **350**, 94–98 (2015).
256. Xu, X. et al. Amplicon resequencing identified parental mosaicism for approximately 10% of '*de novo*' *SCN1A* mutations in children with Dravet syndrome. *Hum. Mutat.* **36**, 861–872 (2015).
257. Scheffer, I. E. et al. Mutations in mammalian target of rapamycin regulator *DEPDC5* cause focal epilepsy with brain malformations. *Ann. Neurol.* **75**, 782–787 (2014).
258. Friedman, A. et al. Should losartan be administered following brain injury? *Expert Rev. Neurother.* **14**, 1365–1375 (2014).
259. Devinsky, O. et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N. Engl. J. Med.* **376**, 2011–2020 (2017).
260. Milligan, C. J. et al. *KCNT1* gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann. Neurol.* **75**, 581–590 (2014).
261. Barcia, G. et al. *De novo* gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat. Genet.* **44**, 1255–1259 (2012).
262. Heron, S. E. et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.* **44**, 1188–1190 (2012).
263. Mikati, M. A. et al. Quinidine in the treatment of KCNT1-positive epilepsies. *Ann. Neurol.* **78**, 995–999 (2015).
264. Bearden, D. et al. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann. Neurol.* **76**, 457–461 (2014).
265. Mullen, S. A. et al. Precision therapy for epilepsy due to KCNT1 mutations: A randomized trial of oral quinidine. *Neurology* **90**, e67–e72 (2018).
266. Pitkänen, A. et al. Advances in the development of biomarkers for epilepsy. *Lancet Neurol.* **15**, 843–856 (2016).
This paper provides an excellent overview of diagnostic biomarkers that can inform about the clinical status effects of therapies as well as prognostic biomarkers that can inform about outcome.
267. Sykes, L., Wood, E. & Kwan, J. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. *Cochrane Database Syst. Rev.* **1**, CD005398 (2014).
268. Beghi, E. et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* **51**, 671–675 (2010).
269. Sveinsson, O., Andersson, T., Carlsson, S. & Tomson, T. The incidence of SUDEP. *Neurology* **89**, 170–177 (2017).
270. Devinsky, O. et al. Underestimation of sudden deaths among patients with seizures and epilepsy. *Neurology* **89**, 886–892 (2017).
271. Hesdorffer, D. C. et al. Combined analysis of risk factors for SUDEP. *Epilepsia* **52**, 1150–1159 (2011).
272. Devinsky, O., Hesdorffer, D. C., Thurman, D. J., Lhatoo, S. & Richerson, G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol.* **15**, 1075–1088 (2016).
This article reviews the clinical features and suspected pathophysiologies of SUDEP.
273. de Kovel, C. G. F. et al. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain* **133**, 23–32 (2010).
274. Ricos, M. G. et al. Mutations in the mammalian target of rapamycin pathway regulators *NPRL2* and *NPRL3* cause focal epilepsy. *Ann. Neurol.* **79**, 120–131 (2016).
275. Ishiura, H. et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat. Genet.* **50**, 581–590 (2018).
276. Crompton, D. E. & Berkovic, S. F. The borderland of epilepsy: clinical and molecular features of phenomena that mimic epileptic seizures. *Lancet Neurol.* **8**, 370–381 (2009).
277. Hesdorffer, D. C. Comorbidity between neurological illness and psychiatric disorders. *CNS Spectr.* **21**, 230–238 (2016).
This paper examines the growing evidence linking the reciprocal relationship between epilepsy and psychiatric disorders.
278. Winawer, M. R., Connors, R. & EPGP Investigators. Evidence for a shared genetic susceptibility to migraine and epilepsy. *Epilepsia* **54**, 288–295 (2013).
279. Jentink, J. et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N. Engl. J. Med.* **362**, 2185–2193 (2010).
280. Tomson, T. et al. Pregnancy registries: Differences, similarities, and possible harmonization. *Epilepsia* **51**, 909–915 (2010).
281. Tomson, T. et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol.* **10**, 609–617 (2011).
282. Vajda, F. J., O'Brien, T. J., Graham, J. E., Lander, C. M. & Eadie, M. J. Dose dependence of fetal malformations associated with valproate. *Neurology* **81**, 999–1003 (2013).
283. Vajda, F. J. E. et al. The teratogenic risk of antiepileptic drug polytherapy. *Epilepsia* **51**, 805–810 (2009).
284. Holmes, L. B., Mittendorf, R., Shen, A., Smith, C. R. & Hernandez-Diaz, S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. *Arch. Neurol.* **68**, 1275–1281 (2011).
285. Vajda, F. J. E., O'Brien, T. J., Lander, C. M., Graham, J. & Eadie, M. J. Antiepileptic drug combinations not involving valproate and the risk of fetal malformations. *Epilepsia* **57**, 1048–1052 (2016).
286. Meador, K. J. et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* **12**, 244–252 (2013).
This is a landmark study on how ASDs can affect development and cognitive outcome.
287. Wood, A. G. et al. Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia* **56**, 1047–1055 (2015).
288. Meador, K. J. et al. Breastfeeding in children of women taking antiepileptic drugs. *JAMA Pediatr.* **168**, 729 (2014).
289. Perucca, P. & Mula, M. Antiepileptic drug effects on mood and behavior: molecular targets. *Epilepsy Behav.* **26**, 440–449 (2013).

Author contributions

Introduction (O.D. and I.E.S.); Epidemiology (N.J.); Mechanisms/pathophysiology (A.V., M.d.C. and I.E.S.); Diagnosis, screening and prevention (P.P. and I.E.S.); Management (T.J.O.B.); Quality of life (O.D.); Outlook (I.E.S. and O.D.); and Overview of Primer (O.D.).

Competing interests

O.D. has received research funding from the US NIH, GW Pharmaceuticals, Novartis and PTC Pharmaceuticals. He has equity in Egg Rock Holdings, Empatica, Engage Therapeutics, Pairnomix, Rettco and Tilray. He is the Principal Investigator for the North American SUDEP Registry and the SUDC Registry and Research Collaborative. He currently receives research funding from NIH and the US Centers for Disease Control and Prevention. He consults for the Center for Discovery. A.V. has received consultancy fees from UCB Pharma and research grants from Ovid, Pfizer and Takeda. T.J.O.B. has received research funding from Eisai, the National Health and Medical Research Council of Australia, the NIH, the Royal Melbourne Hospital Neuroscience Foundation and UCB Pharma. N.J. currently receives research funding from Alberta Health, the Canadian Institute of Health Research and the NIH, and is an associate editor of *Epilepsia* and serves on the editorial board of *Neurology*. I.E.S. has served on scientific advisory boards for BioMarin, Eisai, GlaxoSmithKline, Nutricia and UCB Pharma, sits on the editorial boards of *Epileptic Disorders* and *Neurology* and might accrue future revenue on a pending patent. I.E.S. has also received speaker honoraria from Athena Diagnostics, Eisai, GlaxoSmithKline, Transgenomics and UCB Pharma, has received funding for travel from Athena Diagnostics, Biocodex, BioMarin, Eisai, GlaxoSmithKline and UCB Pharma, and has received research support from the American Epilepsy Society, the Australian Research Council, CURE, the Health Research Council of New Zealand, the March of Dimes, the National Health and Medical Research Council of Australia, the NIH, the US Department of Defense Autism Spectrum Disorder Research Program, and Perpetual Charitable Trustees. P.P. has received honoraria from Eisai. All other authors declare no competing interests.

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