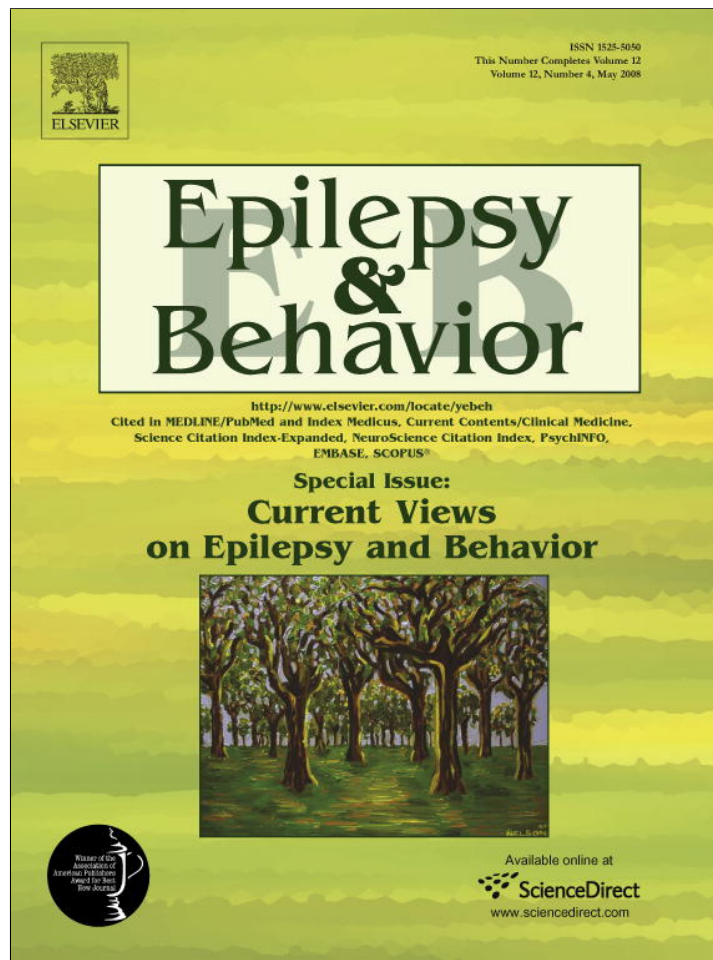


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## Review

# Modern management of epilepsy: A practical approach

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**Abstract**

The epilepsies are among the most common serious brain disorders, can occur at all ages, and are characterized by a variety of presentations and causes. Diagnosis of epilepsy remains clinical, and neurophysiological investigations support the diagnosis of the syndrome. Brain imaging is able to identify many of the structural causes of the epilepsies. Current antiepileptic drugs (AEDs) block seizures without influencing the underlying tendency to generate seizures, and are effective in 60–70% of individuals. Several modern drugs are as efficacious as the older medications, but have important advantages including the absence of adverse drug interactions and hypersensitivity reactions. Epilepsy is associated with an increased prevalence of mental health disorders including anxiety, depression, and suicidal thoughts. An understanding of the psychiatric correlates of epilepsy is important to the adequate management of people with epilepsy. Anticipation of common errors in the diagnosis and management of epilepsy is important. Frequent early diagnostic errors include nonepileptic psychogenic seizures, syncope with myoclonus, restless legs syndrome, and REM behavioral disorders, the last mostly in elderly men. Overtreatment with too rapid titration and too high doses or too many AEDs should be avoided. For people with refractory focal epilepsy, vagus nerve stimulation offers palliative treatment with possible mood improvement and neurosurgical resection offers the possibility of a life-changing cure. Potential advances in the management of epilepsy are briefly discussed. This short review summarizes the authors' how-to-do approach to the modern management of people with epilepsy.

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**Keywords:** Epilepsy; Epilepsy management; Drug treatment; Antiepileptic drugs; Epilepsy surgery; Nonepileptic seizures

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**1. Introduction**

Epilepsies are among the most common of all the serious neurological disorders worldwide. Approximately 4 million persons in the European Union and the United States have epilepsy, and 3% of the general population will have epilepsy at some point in their lives. The modern antiepileptic drug (AED) era—spanning a period of more than 150 years from the first use of bromide in 1857 to 2008—has seen the introduction into clinical practice of a diverse group of effective and safe drugs. These AEDs have provided considerable benefits for those afflicted with epilepsy of all kinds. In as many as 60–70% of newly treated patients, current AEDs lead to satisfactory control of seizures and a favorable risk–benefit balance for the great

majority of patients, albeit with considerable differences in response depending on the type of seizure and epilepsy syndrome and rare serious adverse events. The clinical goal must be the treatment and cure of epilepsy. In this short review, the practical management of epilepsy is briefly summarized from the personal perspective of the authors, with only few references. For an extensive discussion and detailed references, see textbooks, guidelines for the clinical management of individuals with epilepsy, and monographs [1–3].

**2. Definition, diagnosis, and prognosis of epilepsy***2.1. Definition*

The term *epilepsy* encompasses a number of different syndromes, the cardinal feature of which is a predisposition to recurrent unprovoked seizures [for discussion, see 4].

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Seizures, in turn, are sudden, brief attacks of altered consciousness; motor, sensory, cognitive, psychic, or autonomic disturbances; or inappropriate behavior caused by abnormal excessive or synchronous neuronal activity in the brain [see 4]. The phenotype of each seizure is determined by the point of origin of the hyperexcitability and its degree of spread in the brain. By convention, the diagnosis of epilepsy requires that the patient has had at least two unprovoked seizures. The estimated incidence is one case per 2000 persons in the Western population per year, whereas the prevalence of active epilepsy with recent seizures is around 5–10 per 1000. For unknown reasons, the incidence of epilepsy is highest in the first year of life and increases again for those over 60 years of age. The cumulative incidence, that is, the chance of having epilepsy during a lifetime of 80 years, is about 3% [5]. If given a sufficient stimulus (e.g., hypoxia, convulsant agents, hypoglycemia), even the normal brain can discharge excessively, producing a seizure. However, a person with isolated nonrecurrent, externally provoked seizures that are also caused by excessive discharge of cerebral neurons is not thought to have epilepsy as long as the seizures are not recurrent and each seizure is preceded by a provocation (e.g., substance abuse, fever, exposure to alcohol combined with lack of sleep). The distinction is, however, tenuous and must be retrospective, as epilepsy always begins with a first seizure and, albeit uncommon, seizures may be precipitated in persons with epilepsy by exogenous factors, such as sound, light, and touch. Often, the epilepsy syndrome allows the diagnosis of epilepsy even after a first seizure.

## 2.2. Pathophysiology

Current theories try to explain the mechanism(s) for the abnormally increased propensity of the brain to develop excessive discharges of cerebral neurons. The early theory according to which disruption of the normal balance between excitation and inhibition in the brain results in seizure generation may have been an oversimplification. Cortical networks that generate oscillations, on which inhibitory neurons, neuronal communication (e.g., synaptic transmission), and intrinsic neuronal properties (e.g., ability of a neuron to maintain burst firing) are dependent, are thought to be crucial elements of seizure generation. The occurrence of epileptic activity may be an emergent property of such oscillatory networks [6]. Transition from normal behavior to a seizure behavior may be caused by a number of factors including greater spread and neuronal recruitment secondary to a combination of enhanced connectivity, enhanced excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties [7].

### 2.2.1. Generalized epilepsies

Generalized epilepsies result in seizures occurring throughout the cortex because of a generalized lowering of the seizure threshold, and are usually genetically determined. Mutations in voltage-gated potassium, sodium, and chloride

channels, as well as in ligand-gated acetylcholine and GABA<sub>A</sub> ( $\gamma$ -aminobutyric acid, subunit A) receptors, are known to cause different forms of idiopathic epilepsy. All but one of the idiopathic epilepsies with a known molecular basis are channelopathies. Where the ion channel defects have been identified, however, they generally account for a minority of families and sporadic cases with the syndrome in question. The data suggest that ion channel mutations of large effect are a common cause of rare monogenic idiopathic epilepsies, but are rare causes of common epilepsies. Additive effects of genetic variation, perhaps within the same ion channel gene families, are likely to underlie the common idiopathic generalized epilepsies with complex inheritance. A clinical syndrome often has multiple possible genetic causes, and conversely, different mutations in one gene can lead to various epileptic syndromes. Most common epilepsies, however, are probably complex traits with environmental effects acting on inherited susceptibility, mediated by common variation in particular genes [7].

Absence seizures are a distinct form of generalized seizure generated by thalamocortical loops [8]. Absences were originally believed to be generated subcortically by thalamic neurons driving recruitment of neocortical neurons. However, paroxysmal oscillations within thalamocortical loops in absence seizures in rats seem to originate in the somatosensory cortex rather than the thalamus, with synchronization mediated by rapid intracortical propagation of seizure activity [8]. Together with neuroimaging findings of subtle cortical structural abnormalities in some patients with absence seizures and in patients with juvenile myoclonic epilepsy, and the well-known potential of focal pathological change in the medial frontal lobe to generate absence-like seizures, the distinction between focal and generalized epilepsies has become more difficult.

### 2.2.2. Partial (focal, localization-related) epilepsies

In focal epilepsies, focal functional disruption—often due to focal pathological changes (e.g., tumor) or, rarely, to a genetic diathesis (e.g., autosomal dominant frontal lobe epilepsy)—results in seizures beginning in a localized fashion; these seizures then spread by recruitment of other brain areas. The site of the focus and the speed and extent of spread determine the clinical manifestation of the seizure. Intensive studies of hippocampal sclerosis, the most common pathological finding in adults with the most common partial epilepsy, have demonstrated many local changes, but their causative role, if any, in epileptogenesis is still unknown. Newer avenues of study (such as cortical malformations) and newer conceptual mechanisms (such as the role of glial cells, the neuronal microenvironment, and emergent complex network properties) are likely to yield further insights into this complicated field. For now, however, although prevention remains elusive, our clinical goals must remain the treatment and cure of epilepsy [9].

To complicate things further, current AEDs suppress seizures without influencing the underlying tendency to

generate seizures, suggesting that the process of seizure generation, which may be different for each seizure type, and the cellular and molecular mechanisms that determine the underlying tendency to generate seizures may not be identical. Despite important advances in recent years, our understanding of the cellular and molecular mechanisms by which epilepsy develops, or epileptogenesis, is still incomplete. For further discussion, see Refs. [2,3].

### 2.3. Clinical diagnosis

The first seizure that brings a patient to the attention of a physician is usually a tonic–clonic seizure. If there is no suggestion of a provoked seizure or an acute cause, including substance abuse, lack of sleep, and medical disease, early-stage epilepsy is likely. Particularly in those who seem to have had several unprovoked tonic–clonic seizures, a careful history will often bring to light additional seizures such as absence, myoclonic, and, more often, complex partial seizures, which not only confirm the diagnosis of epilepsy but often allow diagnosis of the epilepsy syndrome. The diagnosis of a seizure can be made clinically in most cases by obtaining a detailed history and performing a general clinical examination with emphasis on neurological and psychiatric status. An eyewitness account of a typical seizure(s), age and external circumstances at onset, frequency of each type of seizure, and longest and shortest intervals between them should be recorded. A seizure diary helps to ascertain treatment response. The history should cover the existence of prenatal and perinatal events, spontaneous abortions, seizures in the newborn period, febrile seizures, any unprovoked seizures, and epilepsies in the family (Checklist 1.1). The existence of an aura should be ascertained, and conditions that may have precipitated the seizure in the opinion of the patient should be documented. A history of prior head trauma, infection, or toxic episodes must be sought and evaluated. A family history of seizures or neurological disorders is significant.

### 2.4. Appropriate studies

Once the seizures are classified (e.g., simple, complex partial, partial-onset GTC or generalized absence, myoclonic seizure or generalized-onset GTC) and, if possible,

#### Checklist 1.1

##### History taking in a patient with new-onset epilepsy

Patient: Seizure onset, course, time of day. Earlier seizures? Postictal paresis, aphasia, speech problem, tongue bite, tiredness?

Observer: Onset, course, duration, eyes open or closed, facial color, facial and upper chest petechiae. Postictal speech, paresis, confusion and its duration, behavior?

Physician: Caution: Frequent early diagnostic errors include non-epileptic psychogenic seizures, convulsive syncope with myoclonus, and REM behavioral disorder, the latter mostly in elderly men (see non-epileptic seizures). If in doubt that it is epilepsy, better wait for confirmation through EEG or by observing another seizure. A delayed diagnosis usually causes no problem, while a premature and erroneous diagnosis of epilepsy may have grave implications.

the epilepsy (idiopathic or symptomatic) or the epilepsy syndrome (e.g., temporal lobe epilepsy, generalized juvenile myoclonic epilepsy) is classified, appropriate studies are ordered including an electroencephalogram (EEG) (Fig. 1), magnetic resonance imaging (MRI) (Fig. 2 and Table 1), and serum glucose, sodium, magnesium, and calcium levels (Checklist 1.2). The EEG between seizures (interictal) in primarily generalized tonic–clonic seizures is characterized by symmetric bursts of sharp and slow, 4- to 7-Hz activity. Focal epileptiform discharges occur in secondarily generalized seizures. In absence seizures, spikes and slow waves appear at a rate of 3/second. Interictal temporal lobe foci (spikes or slow waves) occur with complex partial seizures of temporal lobe origin. Because an EEG taken during a seizure-free interval is normal in 30% of patients, one normal EEG does not exclude epilepsy. A second EEG performed during sleep in sleep-deprived patients reveals epileptiform abnormalities in half of patients whose first EEG was normal. Rarely, repeated EEGs are normal, and epilepsy may have to be diagnosed on clinical grounds. When the seizures are focal or an EEG is focally abnormal, when seizures begin in adulthood, or the physical examination reveals focal pathological symptoms or signs, MRI is indicated to detect structural lesions caused by, for example, cortical malformation, traumatic brain injury, brain tumor, and cerebrovascular disease, which are the most common causes of symptomatic epilepsy. In our view, MRI is also useful in generalized epilepsy or generalized seizures to search for dual pathology, for example, an unsuspected brain lesion [10]. A lumbar puncture should be performed if fever and stiff neck accompanying new-onset seizures suggest meningitis, subarachnoid hemorrhage, or encephalitis.

*Recommendation. Every patient with a newly diagnosed epilepsy should undergo MRI to identify structural causes of epilepsy and an EEG to assist in the diagnosis of the syndrome. If the first EEG is normal, order an EEG during sleep; if the first MRI scan is normal, repeat in the case of drug-resistant epilepsy as a first step to explore surgical options.*

### 2.5. Classification of seizures

The academic classification of phenotypical epileptic seizures is constantly evolving. Seizures may be classified by their semiology as partial or generalized (Fig. 3) [11]. In partial seizures, the excess neuronal discharge is thought to originate within one region of the cerebral cortex. In generalized seizures, the discharge bilaterally and diffusely involves the entire cortex. If the focal discharge spreads rapidly, it may produce a generalized tonic–clonic seizure before a focal manifestation is noted (Fig. 3).

#### 2.5.1. Practical implications

For practical purposes, however, it is sufficient to be able to distinguish between generalized absence and particularly myoclonic seizures and partial seizures before start-

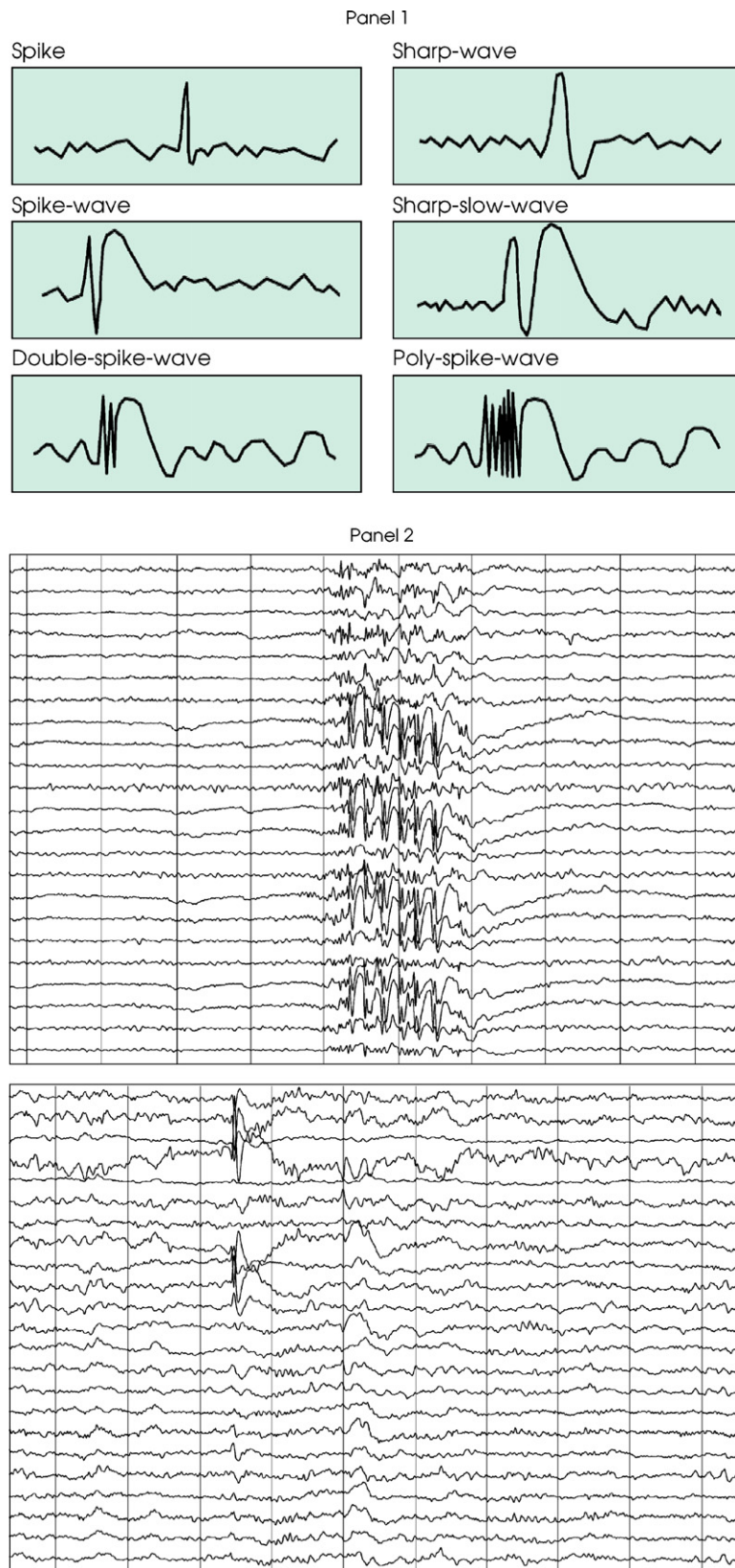


Fig. 1. Electroencephalography. Panel 1: Interictal discharges are distinctive waves or complexes that can be recorded between seizures in the EEGs of individuals with epilepsy. Generally brief in duration, they may have a variety of morphologies described as sharp wave, spike wave, or spike-and-slow wave. Panel 2, top: A generalized discharge of bilateral spike-and-wave activity, predominantly in the frontal region. Panel 2, bottom: Single sharp-slow-wave, right mesial temporal region.

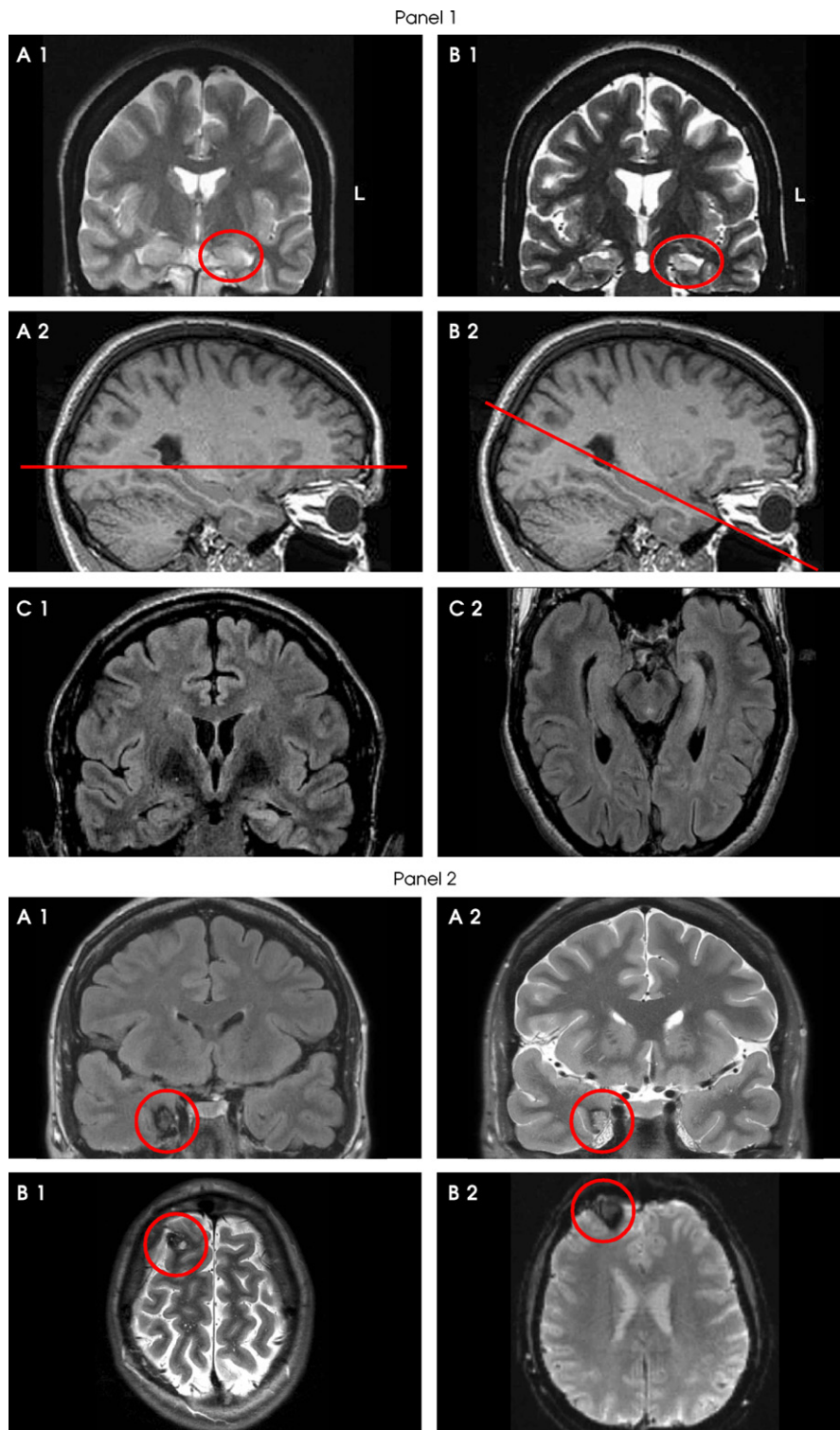


Fig. 2. Magnetic resonance imaging (MRI) in epilepsy. Panel 1: A1, Ammonshornsclerosis left, standard coronal angulation; A2, standard coronal angulation; B1, Ammonshornsclerosis (syn.: mesial temporal sclerosis) left, coronal temporal angulation; B2, coronal temporal angulation; C1, flair sequence coronal and axial, temporal angulation. Panel 2: Cavernoma; A1, mesio-temporal right, flair sequence; A2, T2 weighted; B1, frontal right, T2 weighted; B2, T2\* weighted (pronounced effect of old blood). Panel 3: Developmental tumors A, dysembryoplastic neuroepithelial tumor; temporo-lateral right, B1,2, ganglioglioma temporo-mesial right. Panel 4: Chronic inflammation; A 1,2 = nc. amygdala right; B 1,2, Rasmussen's Encephalitis, left hemisphere. Panel 5: A1,2, Hypothalamic hamartoma. Panel 6: Cortical developmental abnormality left parietal (A+B) and occipital C (cortical dysplasia Type IIb (Palmini): A1, T2 weighted axial; B2, flair sequence coronal; A2, flair sequence coronal; B1, flair sequence coronal; B2, inversion recovery sequence coronal. C1, T2 weighted; C2, flair sequence (C: courtesy of Department of Radiology, University Bonn, Germany).

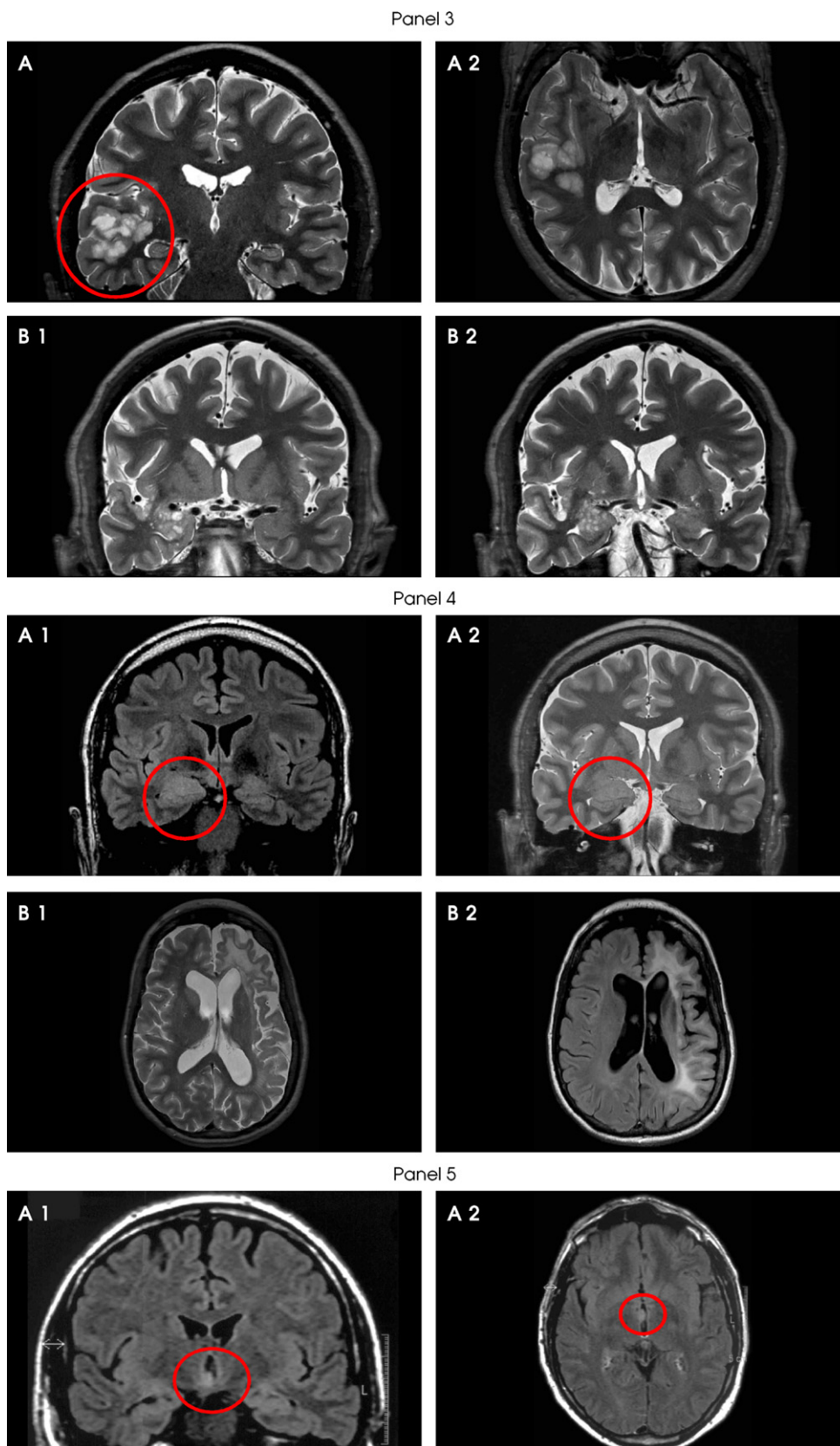


Fig. 2 (continued)

ing AED treatment. The main reason is that some AEDs that are useful in treating partial seizures and secondarily

generalized GTCs, such as carbamazepine (CBZ), gabapentin (GBP), oxcarbazepine (OXC), phenytoin (PHT),

Panel 6

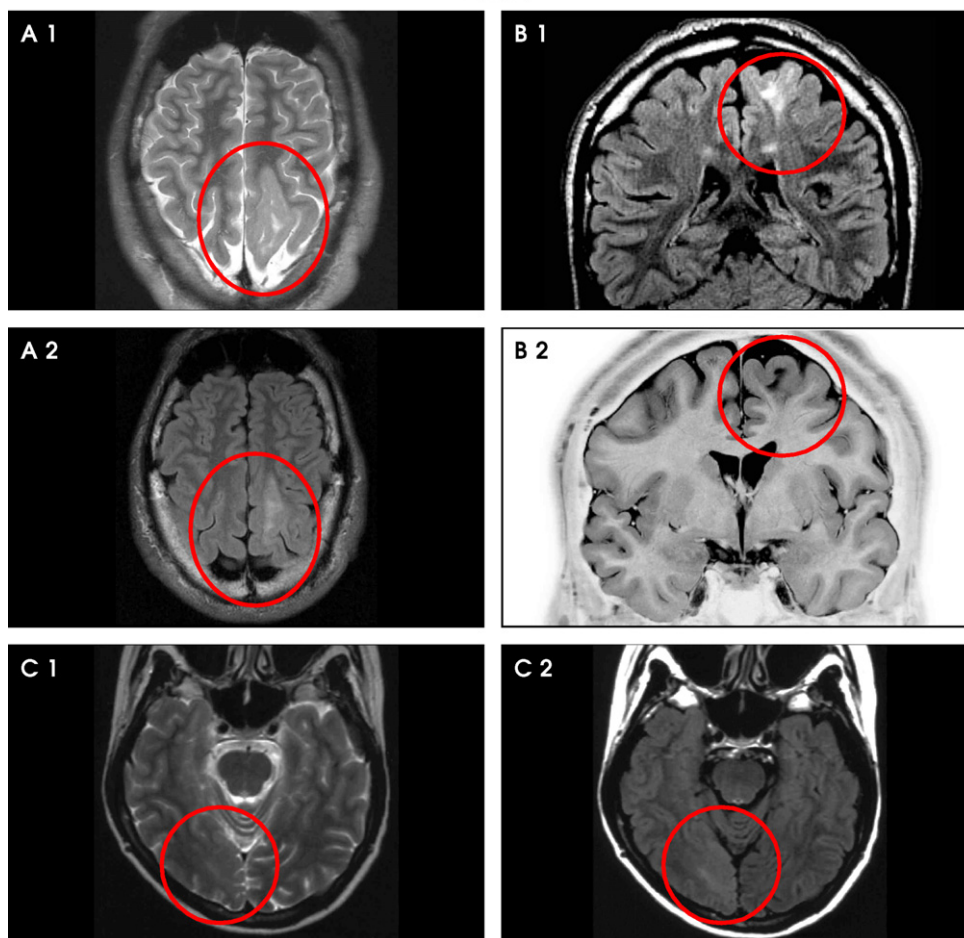


Fig. 2 (continued)

Table 1  
Suggested MRI protocols for epilepsy patients (standard investigations)

Temporal lobe epilepsy	<ol style="list-style-type: none"> <li>1. Hippocampal oriented T2-weighted (coronal + axial)</li> <li>2. Hippocampal oriented fluid-attenuated inversion recovery (FLAIR) (coronal + axial)</li> <li>3. Isotropic T1-weighted three-dimensional sequence (MPRage)</li> <li>4. (Gadolinium contrast-enhanced T1-weighted image if non-contrast-enhanced image is inconclusive)</li> <li>5. T2<sup>*</sup>-weighted sequence</li> </ol>
Extratemporal lobe epilepsy	<ol style="list-style-type: none"> <li>1. AC–PC oriented T2-weighted (coronal + axial)</li> <li>2. AC–PC oriented FLAIR (coronal + axial)</li> <li>3. Isotropic T1-weighted three-dimensional sequence (MPRage)</li> <li>4. (Gadolinium contrast-enhanced T1-weighted image if non-contrast-enhanced image is inconclusive)</li> <li>5. T2<sup>*</sup>-weighted sequence</li> </ol>
Special protocols: Rationale	<ol style="list-style-type: none"> <li>1. T2 relaxometry hippocampal signal abnormalities</li> <li>2. Magnetic resonance spectroscopy detection of metabolic abnormalities</li> <li>3. Diffusion tensor imaging (DTI) investigation of fiber tracts</li> <li>4. Functional MRI investigation of eloquent cortical areas</li> <li>5. Three-dimensional sequences automated voxel-based analyses</li> <li>6. Magnetic resonance angiography investigation of brain vascularization</li> </ol>

and pregabalin (PGN), may not work or may even exacerbate absence or myoclonic seizures. On the other hand, ethosuximide (ETS), which is useful but seldom used these

days to treat absence seizures, is clearly not efficacious against other seizure types. A number of AEDs are useful for both partial and generalized absence or myoclonic sei-



Checklist 1.2

Studies in patient with new-onset epilepsy

**MAGNETIC RESONANCE IMAGING (MRI):** Each patient with new-onset epilepsy should have an MRI (temporal angulation, T1,T2, FLAIR, coronal and axial) to detect structural lesions caused by for example cortical malformation, traumatic brain injury, brain tumor, and cerebrovascular disease, which are the most common causes of symptomatic epilepsy. Contrast media, inversion recovery, fast field echo and 3D only in special cases. Even in idiopathic epilepsy, MRI is recommended to diagnose unsuspected dual pathology as discussed above.

**ELECTROENCEPHALOGRAM (EEG):** Each patient with new-onset epilepsy should have an EEG. EEG is most valuable within 24 h of the seizure. Information gain is optimal up to the 4<sup>th</sup> EEG, if no paroxysmal interictal discharges are found, repeat EEG during sleep. 24-hour EEG most meaningful in a patient with frequent seizures who can be expected to have seizures during the 24 h recording. Icteric EEG discharges may support the diagnosis of the epilepsy syndrome.

**COMPUTER TOMOGRAM (CCT):** Computer tomograms are obsolete, except to detect fractures or hemorrhage in an emergency situation.

**HEAD X-RAY:** obsolete

**CLINICAL CHEMISTRY:** routine work-up, creatin kinase, Vitamin B6 if seizures are unresponsive to AEDs, even in adults. CSF, only when infectious disorders are suspected. Creatin kinase increased within 12-24 h, prolactin increased within 30 min.

**SINGLE-PHOTON-EMISSION-TOMOGRAM (SPECT) and POSITRON-EMISSION-TOMOGRAM (PET), MAGNETO ENCEPHALOGRAPHY (MEG):** only for presurgical work-up or scientific studies.

zures and unclassifiable seizures. These are valproate and some of the newer AEDs such as lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM, only for primary GTC seizures), and zonisamide (ZNS). Phenobarbital (PHB) and primidone (PRM) may be useful in treating myoclonic seizures, but may worsen or exacerbate absence seizures. The role of levetiracetam and zonisamide in treating

absence and myoclonic seizures is not fully explored as of now.

2.5.2. *Partial (focal) seizures*

Both simple and complex partial seizures result from a localized brain disturbance; also referred to as focal seizures, these seizures may evolve into secondarily GTC seizures [see 4]. The site of dysfunction determines the clinical manifestation of partial seizures. Examples are: chewing movements or smacking of lips (anterior temporal lobe dysfunction), complex automatic behavior (temporal lobe, anteromedial temporal lobe), visual hallucinations with formed images (posterior temporal lobe), bilateral tonic posture (supplementary motor cortex, frontal lobe), localized twitching of muscles without impaired consciousness in a Jacksonian seizure (motor cortex, frontal lobe), localized numbness or tingling (sensory cortex, parietal lobe), and visual hallucinations with flashes of light (occipital lobe).

2.5.3. *Generalized seizures*

Generalized seizures may impair consciousness and cause bilateral motor manifestations from the onset. Such attacks often have a genetic or metabolic cause. They may be primarily generalized (bilateral cerebral cortical involvement at onset) or secondarily generalized (local cortical onset with subsequent bilateral spread). Common types of generalized seizures include absence, tonic-clonic, and myoclonic seizures [11].

2.5.4. *Unclassifiable seizures*

Unclassifiable seizures are seizures that are impossible to classify as either focal or generalized based on their clinical or EEG manifestations (e.g., atonic, tonic, and tonic-clonic seizures without noticeable focal onset). This term is also used for those seizures in patients whose epilepsy has par-

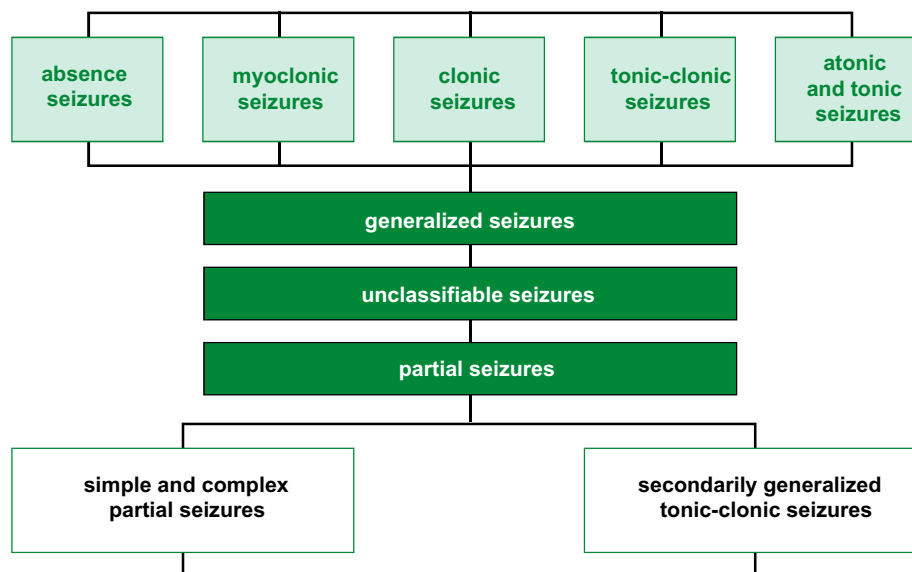


Fig. 3. International classification of epileptic seizures.

tial and generalized elements because of focal and generalized EEG findings. *Atonic seizures* are brief, often but not always generalized seizures in children. They are characterized by complete loss of muscle tone and consciousness. The child falls or pitches to the ground, so that seizures pose the risk of serious trauma, particularly head injury. They may, however, be indistinguishable, even for an experienced observer, from a tonic seizure with a very rapid

focal onset. In the absence of unequivocal evidence from Video/EEG-EMG recordings, the existence of atonic seizures is still a matter of debate, at least for some experts.

#### 2.5.5. Nonepileptic seizures

Frequent early diagnostic errors include nonepileptic psychogenic seizures, convulsive syncope with myoclonus,

#### Checklist 1.3

##### Common non-epileptic seizures

**PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES)** are paroxysmal events that superficially resemble epileptic seizures, which are, however, not caused by epileptic neuronal discharges but by psychopathological processes. Comparative and observational studies show that traumatic childhood experiences (especially sexual and physical abuse), trauma in adulthood, poor family relationships, psychiatric comorbidity, personality disorder, organic brain pathology, low social status as well as financial and social gain can play a predisposing, precipitating or perpetuating role. This suggests that PNES are not a unitary pathological entity but an expression of a number of different psychosocial and psychiatric disorders. PNES are best classified as manifestations of an underlying psychiatric disorder. Consequently, therapy has to be designed to suit individual patients or certain patient groups. It often requires the collaboration of a multidisciplinary team. The prognosis of PNES is determined by the underlying psychosocial problem or disorder. The preliminary observational evidence suggests that specific psychotherapies and pharmacotherapy with serotonin reuptake inhibitors directed at comorbid conditions may be the most effective treatment for PNES. Successful long-term treatment is difficult.

**SYNCOPE** Diagnosing syncope is a great challenge in clinical medicine. Since patients usually do not have symptoms and signs during the interval, the diagnosis is primarily based on a meticulously taken history, if possible also from bystanders, which is particularly important when the patient's recollection is incomplete. The first step is to find out whether or not the patient transiently lost consciousness (i.e. has an amnesic gap), fell to the ground (if upright), and whether he showed convulsive manifestations. Additional features are: Predisposing factors (e.g. occurring only in upright position, drugs, sleep deprivation), prodromal sensations (stereotyped or not), eye open during onset, upward gaze, gentle or violent fall, oral and limb automatisms, tonic and/or clonic manifestations (bilateral - rhythmical or irregular), phonations (unintelligible sounds or vocalizations), color of the face (normal, pale, or cyanotic), loss of urine (but not discriminative), and the postictal behavior and recovery of orientation. A lateral tongue bite must be searched for and is very suggestive of an epileptic seizure, while a median tongue bite is seen with non-epileptic psychogenic seizures. To distinguish between epileptic seizure and circulatory syncope is often difficult, since the latter frequently shows, contrary to common belief, a stiff backward fall and short tonic and clonic and manifestations. Conversely, epileptic falls are not always convulsive. Psychogenic 'pseudo-seizures' are identified by the typical eye closure from the beginning and the long duration of the seizure of over 5 minutes, which are both very rare in epileptic seizures or syncope.

**REM BEHAVIORAL DISORDER** REM sleep behavior disorders (RBD) are episodes of motor agitation arising during REM sleep due to the absence of muscular atonia and are characterized by more or less purposeful gestures enacting attack or defense reactions, sometimes associated with emotional expressions of joy, laughter or sorrow. They occur often in elderly men. RBD often herald other signs and symptoms of neurodegenerative disorders like Parkinsonian syndromes. If correctly diagnosed, they can be treated successfully.

**RESTLESS LEGS** Restless legs syndrome (RLS) is characterized by deep ill-defined paraesthesias in the legs arising during postural rest, especially when the patient is trying to fall asleep. Motor agitation of the legs is associated with periodic involuntary movements, named nocturnal myoclonus (NM) or periodic limb movements in sleep (PLMS). NM may appear independently of RLS and can induce sleep fragmentation, but not necessarily an insomniac complaint.

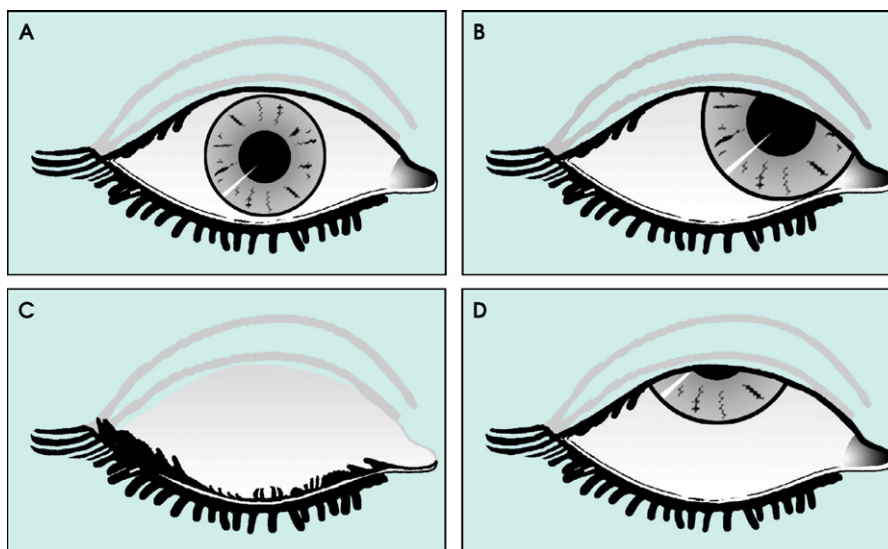


Fig. 4. Eye closure and gaze in various epileptic and nonepileptic seizures. A, Staring during a temporal lobe seizure; B lateral gaze during an extratemporal lobe seizure; C, closed eyes during a psychogenic, non-epileptic attack, D, upward gaze during a syncope.

Table 2  
Clinical features of epileptic seizures versus psychogenic nonepileptic seizures

Clinical feature	Epileptic seizures	Psychogenic nonepileptic seizures
Eyes closed	Uncommon	Very common
Stereotyped seizure semiology	Common	Less common
Seizure duration >2 minutes	Uncommon	Not uncommon
Seizure onset at sleep	Not uncommon	Uncommon
Enuresis	Not uncommon	Uncommon
Injury, burns	Not uncommon	Uncommon
Medial tongue bite	Uncommon	Not uncommon

restless legs syndrome, and REM behavioral disorder, mostly in elderly men [12] (see Checklist 1.3).

For differential diagnosis, one strategic question is whether the eyes are open or closed at the onset of the attack (Fig. 4). Closed eyes are typical of nonepileptic psychogenic seizures (Table 2). In contrast, a staring gaze is characteristic of temporal lobe seizures. A lateral gaze is often seen with extratemporal lobe seizures, for example, frontal lobe seizures. An upward gaze is often observed in patients having a syncopal episode.

*Recommendation. Classification of paroxysmal events into partial seizures, generalized seizures, unclassifiable seizures, and nonepileptic seizures can be difficult in some cases and, for patients with frequent seizures, videoEEG monitoring is advisable. A movie of the seizure taken with a mobile phone is often helpful. Eyes are closed in nonepileptic psychogenic seizures, whereas syncope is frequently characterized by an upward gaze. Unless and until an epileptic seizure is firmly diagnosed and classified, the diagnosis of epilepsy and treatment should be deferred, if possible.*

## 2.6. Classification of epilepsies

Pragmatically, epilepsies can be classified in several ways, as either generalized or partial (or localization-related) and idiopathic or symptomatic (Fig. 5) [13]. In generalized epilepsies, the predominant type of seizure begins simultaneously in both cerebral hemispheres. Many forms of generalized epilepsy have a strong genetic component; in most, neurological function is normal. In partial epilepsies, by contrast, seizures originate in one or more localized foci, although they can spread to involve the entire brain. Most partial epilepsies are believed to be the result of one or more central nervous system insults, but in many cases the nature of the insult is never identified. The other division separates epilepsies with demonstrable etiologies (symptomatic epilepsies) from those with a presumable genetic basis where no symptomatic etiology can be found (idiopathic epilepsies). For pragmatic classification, idiopathic epilepsy must be distinguished from symptomatic epilepsy, and partial epilepsy must be distinguished from generalized epilepsy. In clinical practice, epilepsy syndromes are conveniently divided in those that begin in childhood, adolescence, middle age, and old age. Pragmatically, one should be able to distinguish between epilepsy syndromes that in general are easy to treat and those with

mixed outcome and finally catastrophic epilepsy syndromes. Also, the rate of seizure recurrence after AED discontinuation in seizure-free patients differs considerably among various epilepsy syndromes; for example, the risk is moderate in pediatric idiopathic partial and childhood absence syndromes, but prohibitively high in idiopathic juvenile myoclonic epilepsy and symptomatic epilepsy, particularly with adult onset. Epilepsy syndromes also differ considerably in their prognosis for cognition, memory, and mortality. For further discussion, see [2,3].

*Recommendation. Pragmatically, a syndrome diagnosis of epilepsy is advisable, because the seizure prognosis varies for different syndromes. In any case, the diagnosis of an idiopathic generalized epilepsy should be excluded before starting treatment with an AED useful only for partial seizures. If in doubt, an AED that works against partial and absence or myoclonic seizures should be considered.*

### 2.6.1. Symptomatic epilepsies

The causes of sporadic or recurrent seizures are numerous, and they include acquired structural brain damage, altered metabolic states and inborn brain malformations. Among the partial epilepsies alone, the diversity of demonstrated causes is bewildering, raising the concern that the underlying mechanisms are equally diverse and that no single drug could prevent all forms of partial epilepsy. However, one feature common to the diverse partial epilepsies of humans is a latent period from the time of injury to the first seizure, which may be several months (e.g., after traumatic brain injury) to several years and even one or two decades (e.g., in cases with cortical malformations). By targeting plasticity mechanisms that underlie the enhanced seizure susceptibility that often follows brain insults such as head trauma, status epilepticus, or neonatal hypoxia, antiepileptogenic drugs of the future would prevent, or reverse, progressive worsening of the epileptic process. Currently, however, only surgical resection of epileptogenic brain offers the chance to reverse epilepsy that has not fully responded to AED treatment (see below).

### 2.6.2. Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) represents the majority of the partial symptomatic/cryptogenic epilepsies. Excellent results after epilepsy surgery in well-selected patients have encouraged the search for localizing and lateralizing signs that could assist in the identification of the best surgical

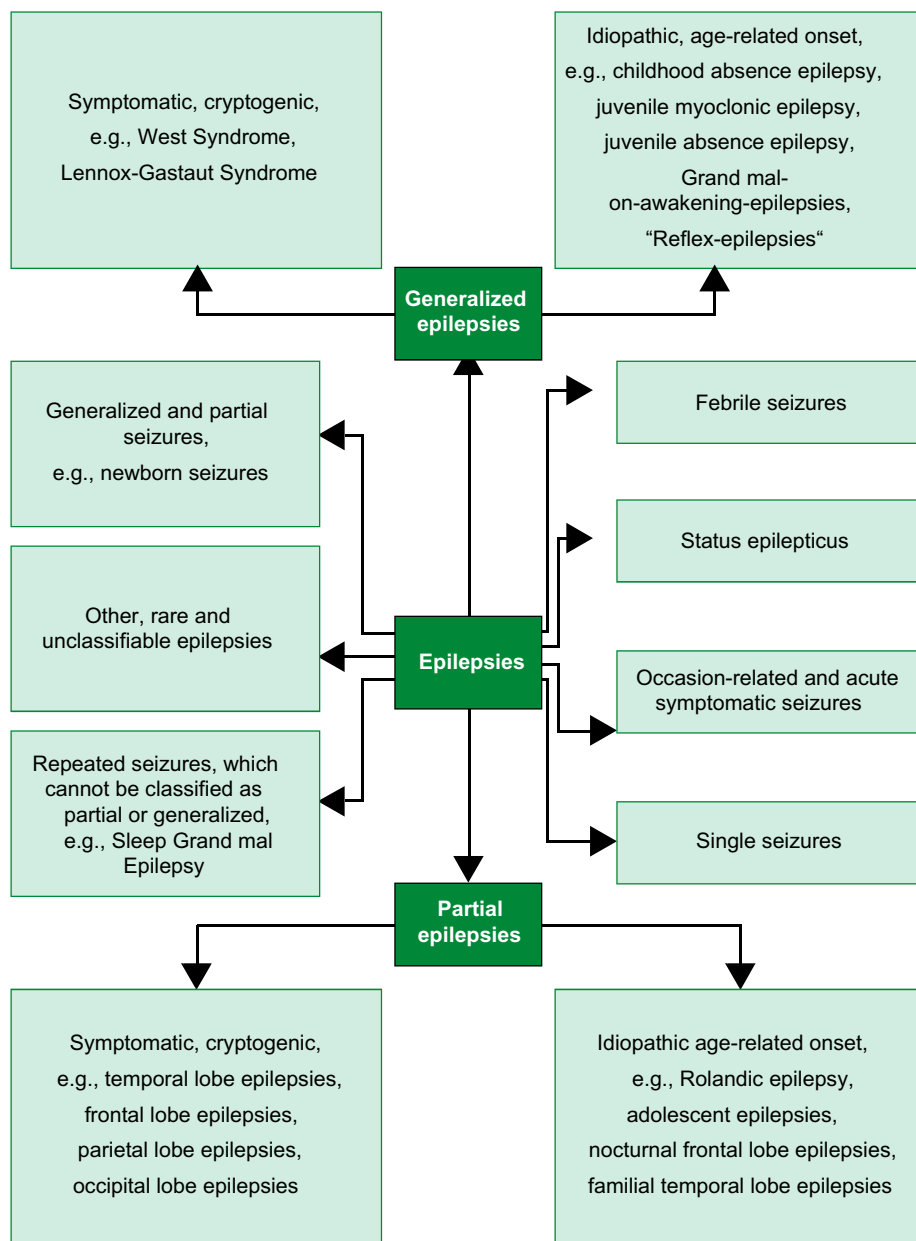


Fig. 5. International classification of epilepsies and epileptic syndromes.

candidates. Seizure types in TLE include simple partial, complex partial, and secondarily generalized seizures. In TLE, seizures most often arise in the amygdalohippocampal region of the mesial temporal lobe; hence the most common partial epilepsy is called mesial temporal lobe epilepsy.

### 2.6.3. Mesial temporal lobe epilepsy

More than 90% of patients with mesial TLE report an aura, most commonly an epigastric sensation that often has a rising character. Other autonomic symptoms, psychic symptoms, and certain sensory phenomena such as olfactory sensations also occur. The complex partial seizures

of mesial TLE often involve motor arrest, orolimentary automatisms, or nonspecific extremity automatisms at onset. Ictal manifestations that have lateralizing value include dystonic posturing (contralateral), early head turning (usually ipsilateral), and adversive head turning in transition to generalization (contralateral). Well-formed ictal language favors right temporal localization. Ictal vomiting, spitting, and drinking tend to be right-sided. In TLE, complex partial seizures generally last 1–2 minutes and postictal confusion usually occurs. When postictal aphasia is noted, a left-sided lateralization is favored. Men with mesial TLE with hippocampal sclerosis more often have secondarily GTC seizures, whereas women have isolated

auras and a lateralized EEG seizure pattern more often, suggesting that seizure spread is more extended or occurs more frequently in men than in women. Our current knowledge of mesial TLE is extensive, yet still insufficient to draw final conclusions on the optimal approach to its therapy. Mesial TLE has been well characterized and can usually be identified with noninvasive studies including scalp electroencephalography and video monitoring with ictal recording, MRI, SPECT, positron emission tomography, neuropsychological assessment, and historical and clinical data. Sometimes, invasive EEG is needed to confirm mesial temporal lobe seizure onset, which, combined with the underlying pathological abnormality (the substrate) of mesial temporal sclerosis (hippocampal neuronal loss and gliosis), defines mesial TLE. This disorder is the most common refractory partial epilepsy, and also the one most often treated surgically, because medical treatment fails in 75% of cases, and surgical treatment with continued drug treatment succeeds in a similar percentage.

#### 2.6.4. Lateral temporal lobe epilepsy

A lateral temporal onset is less common (lateral TLE), and is most often suggested by an auditory aura. Somatosensory and visual auras are highly unlikely with TLE, and suggest neocortical extratemporal localization. A cephalic aura is nonspecific, but is more common in frontal lobe epilepsy.

#### 2.6.5. Frontal lobe epilepsy

Seizures are usually brief (30 seconds to 2 minutes), stereotypic, often nocturnal, and frequent, for example, 3–22 per night, occurring during slow wave sleep. Clinical features include explosive onset, screaming, agitation, stiffening, kicking or bicycling of the legs, and incontinence. Nocturnal frontal lobe epilepsy (NFLE) represents a spectrum of clinical manifestations, ranging from brief, stereotyped, sudden arousals, often recurring several times per night, sometimes with a quasi-periodic pattern, to more complex dystonic–dyskinetic seizures and to prolonged “somnambulant” behavior. Episodes of increasing intensity have been labeled as paroxysmal arousal, nocturnal paroxysmal dystonia, and episodic nocturnal wandering. NFLE affects both sexes with a higher prevalence for men, is frequently cryptogenetic, and displays a strong familial trait for parasomnias and epilepsy. Seizures occur more frequently between 14 and 20 years of age, but can affect persons at any age and tend to increase in frequency during life. Interictal and ictal EEGs are usually normal; the use of sphenoidal leads may be helpful. Long-term video/EEG monitoring may demonstrate frontal or bifrontal epileptic discharges. MRI is normal in many patients. The condition is often misdiagnosed as a sleep disorder or psychiatric problem. Carbamazepine taken at night is often effective at low doses, but a third of patients are resistant to AED treatment. Seizures are difficult, with only half the patients being controlled on carbamazepine or valproic acid. Epilepsy surgery is an option. Autosomal dominant

NFLE is a genetic variant of NFLE, in itself both clinically and biologically heterogeneous. NFLE should be suspected in the presence of frequent stereotyped paroxysmal nocturnal motor events arising or persisting into adulthood. Video/polysomnography is mandatory to confirm the diagnosis.

#### 2.6.6. Idiopathic epilepsies

About 1% of all people develop recurrent unprovoked seizures for no obvious reason and without any other neurological abnormalities. These are named generalized or focal *idiopathic epilepsies*, generalized or partial, and they are assumed to be mainly genetic in origin [4,11]. So far, little is known about the genes that underlie epileptogenesis in idiopathic generalized epilepsies (IGEs). In addition to the large group of idiopathic epilepsies, more than 200 single-gene disorders are known in which epilepsy is a more or less important part of the phenotype. These include syndromes as diverse as neurodegenerative disorders from the group of progressive myoclonus epilepsies, mental retardation syndromes like fragile X syndrome and Angelman's syndrome, neuronal migration disorders, and mitochondrial encephalomyopathies.

#### 2.6.7. Unclassifiable epilepsies

These encompass a number of heterogeneous seizure syndromes that cannot be diagnosed as either partial or generalized, partly because of incomplete data (e.g., tonic and atonic or astatic seizures) or failure to clinically observe the onset of seizures (e.g., tonic–clonic seizures during sleep). In addition, a number of syndromes may be unclassifiable because both partial and generalized seizures may occur (e.g., generalized epilepsy with febrile seizures plus, epileptic encephalopathies, progressive myoclonus epilepsies) [13]. In addition, epilepsies can be classified according to their time of onset in life. Often, all classifications are used to classify an individual epilepsy.

#### 2.6.8. Epilepsies starting in childhood

The childhood-onset epilepsies can be divided into benign, intermediate, and catastrophic based on their impact on childhood development. The clearest benign epilepsy is benign Rolandic epilepsy, which often does not require medication treatment. Although seizures and EEG features usually resolve completely at puberty, neuropsychological deficits and behavior problems are seen in some children. The definition of benign occipital epilepsy including Panayiotopoulos syndrome is still often vague. In the intermediate category, childhood absence epilepsy often has associated learning disorders and a poor social outcome. About 50% of children with cryptogenic partial seizures have a very benign course, even though their epilepsy syndrome is not well defined. Generalized epilepsy with febrile seizures plus (GEFS+) has a dominant inheritance with a defined defect in cerebral sodium channels, but varies considerably in severity within affected members of the same kindred. The catastrophic epilepsies in childhood

all have an inconsistent response to AED treatment and include continuous spike waves in slow sleep (with variable severity), Landau–Kleffner syndrome (with a confusing overlap with autistic regression), Lennox–Gastaut syndrome (with broad defining features), and myoclonic–astatic epilepsy (with important overlaps with Lennox–Gastaut). Although many of the epilepsies that begin in childhood are benign, some interfere seriously with cognitive and social development. Intractable childhood epilepsy may have a negative effect on the mother's mood in many families. Child behavior problems are a strong predictor of maternal depressive symptoms.

#### 2.6.9. *Epilepsies starting during adolescence*

Epilepsy is the commonest serious neurological condition affecting adolescents. Specific epilepsy syndromes begin during adolescence and create a significant neurological burden. Idiopathic generalized epilepsies are the most frequent group with adolescent onset, and juvenile myoclonic epilepsy (JME) is the most common form. This contrasts with a variety of progressive myoclonic epilepsies that also are first seen in adolescence and have a genetic origin and specific treatments. Finally, although mesial temporal lobe epilepsy associated with hippocampal sclerosis may have its origin in childhood, often the child does not come to surgical evaluation until adolescence or young adulthood. The characteristic clinical history, seizure semiology, and MRI findings allow the diagnosis. Applying these same criteria to children and adolescents reveals that hippocampal sclerosis is the most common lesion responsible for their intractable temporal lobe epilepsy. Adolescence is a time of dramatic change in growth, hormonal, psychological, and social situations. Seizure frequency, teenage pregnancy, driving, and alcohol and drug use often become major issues during the adolescent years. Furthermore, adolescents often have difficulty accepting the chronicity of epilepsy and complying with medications, which can result in physical injury and perceived or real obstacles to employment.

#### 2.6.10. *Epilepsies starting in the elderly*

Longer life expectancy in the general population is the reason for the second peak in the incidence of epilepsy in persons 60 and older; the incidence exceeds 1 per 1000 at age 70 and above. Partial seizures in the elderly may be associated more frequently with Todd's paresis, and postictal confusion may last longer than 24 hours and be complicated by prolonged aphasia. De novo absence status may occur, particularly in the elderly with substance abuse. Status epilepticus is associated with a higher mortality in the elderly. The seizure-related risk of injury including fractures is higher in the elderly [14].

#### 2.7. *Status epilepticus*

In status epilepticus, seizures follow one another without recovery of consciousness or intervening periods of

normal neurological function. Generalized convulsive status epilepticus may be fatal. It may result from too rapid withdrawal of anticonvulsants. Confusion may be the only manifestation of complex partial or absence status epilepticus, and an EEG may be needed to diagnose seizure activity. *Epilepsia partialis continua* is a rare form of focal (usually hand or face) motor seizures that recur at intervals of a few seconds or minutes for days to years at a time. In adults, it is usually due to a structural lesion, such as a stroke. In children, it is usually due to a focal cerebral cortical inflammatory process (Rasmussen's encephalitis), possibly caused by a chronic viral infection or autoimmune processes.

*Recommendation.* *The diagnosis of status epilepticus should be made only after unequivocal evidence of epilepsy is obtained; psychogenic status should be suspected in refractory cases, particularly in persons with the following profile: no clear neurological deficit, a psychiatric history, and, surprisingly, a health professional background.*

#### 2.8. *Comorbidity*

Comorbid conditions, including anxiety, suicidal thoughts, depression, cognitive decline, migraine, psychogenic nonepileptic disorders, injuries, and increased mortality are common in patients with epilepsy. In the community, epilepsy is associated with a twofold prevalence of mental health disorders, including anxiety disorders, suicidal thoughts, and major depression, compared with the general population, although the prevalence of panic disorders including agoraphobia is not increased (Table 3) [15].

Depression is estimated to occur in as many as 50% of patients with refractory partial epilepsy, especially of temporal lobe origin. In patients with refractory left temporal lobe epilepsy, memory functions decline 10 years earlier than in age-related controls, and left temporal lobe resection leads to a further decline in verbal memory. Right temporal lobe epilepsy sometimes causes visuospatial memory abnormalities. Although depression is common, and can be treated well with serotonin reuptake inhibitors, it often goes undiagnosed and remains untreated. Other less common psychiatric comorbid conditions include autism, psychosis, and psychogenic nonepileptic seizures. Migraine also seems to be more common in patients with epilepsy, particularly in those with a history of head trauma, partial seizures, and a family history of migraine. Furthermore, endocrine reproductive disorders and sexual dysfunction are more prevalent in persons with epilepsy of either gender. Comorbidity with other conditions may be caused by the epilepsy itself, by adverse events on endocrine function of drug or surgical treatment, overuse of AEDs, and psychosocial factors. Finally, patients with epilepsy also show an increased risk for injury and have a shorter life expectancy, particularly those with refractory epilepsy.

*Recommendation.* *Depression, suicidal thoughts, and anxiety disorders are common comorbid conditions in patients*

Table 3  
Psychiatric comorbidity in people with epilepsy and the general population

Psychiatric disorder (lifetime)	Epilepsy (N = 253)	No epilepsy (N = 36717)
Major depressive disorder	17.4% (10.0–24.9) <sup>a</sup>	10.7% (10.2–11.2)
Mood disorder	24.4% (16.0–32.8)	13.2% (12.7–13.7)
Anxiety disorder	14.1% (7.2–21.1)	11.2% (10.8–11.7)
Mood disorder/anxiety disorder/dysthymia	34.2% (25.0–43.3)	19.6% (19.0–20.2)
Panic disorder/agoraphobia	6.6% (2.9–10.3)	3.6% (3.3–3.9)
Suicidal ideation	25.0% (17.4–32.5)	13.3% (12.8–13.8)
Any mental health disorder	35.5% (25.9–44.0)	20.7% (19.5–20.7)

Source. Modified from Ref. [15].

<sup>a</sup> The 95% confidence interval is given in parentheses.

with epilepsy, particularly in refractory cases. Effective and safe treatment is available.

## 2.9. Prognosis

### 2.9.1. Seizures

Within a year of treatment, drug therapy completely eliminates seizures in one of two patients with new-onset epilepsy and greatly reduces the frequency of seizures in another one of six; in one of three, however, seizures cannot be controlled by AEDs (Fig. 6). It is not well known how often drug resistance, a major clinical problem, occurs early or late in the course of epilepsy and how often epilepsy follows a continuous, remitting, or relapsing–remitting pattern. To provide evidence if, in fact, different patterns of evolution of drug resistance and remission exist, a prospective, long-term population-based study of 144 patients followed for 40 years (median) since their first seizure before the age of 16 was performed. At the end of the follow-up, 67% patients were in terminal 5-year remission, on or off antiepileptic drugs, the remainder will never enter remission (19%), and 14% will have only transient periods of 5-year remission. In 16% of those with terminal remission, first remission continued uninterrupted, whereas half

of those with terminal remission became seizure free only after a delay of 9 years, suggesting improvement over time. However, outcome may worsen over time in 14%, who entered one or more periods of 5-year remission but did not maintain remission at the end of follow-up [16]. This outcome suggests that patients seem to fall broadly into three groups: (1) In 50% of patients, the seizure prognosis is good to excellent. This group includes those with self-limiting epilepsies with few seizures, for whom AEDs may not even be necessary for seizure control, and the first single AED controls the epilepsy; once seizure control is achieved, AEDs may be successfully tapered in many patients. Whether the AEDs suppress or affect the course of epilepsy in this group is unclear. (2) In another 10–20%, seizure prognosis is still good, but there may be a struggle to find the right AED. Seizure control may take years to achieve, and the relapse rate is high whether AEDs are withdrawn or not. Many need drug treatment for life. Surgery may improve the seizure outcome in this group. (3) Up to 30% carry a bad seizure prognosis with a continuous tendency to have seizures. AEDs seem to be palliative rather than suppressant, but new AEDs may improve outcome in some patients. Predictors of good outcome include less than weekly seizures prior to treatment and nonsymptomatic etiology [for review, see 5].

### 2.9.2. Injuries and mortality

Accidents and injuries occur slightly more frequently among people with epilepsy than in the general population, particularly in those with symptomatic epilepsy, frequent seizures, and associated handicaps. The majority of accidents are minor and occur at home. The most frequent injuries among patients with epilepsy are contusions, wounds, fractures, abrasions, and brain concussions. The mortality in population-based studies is two to three times higher for people with epilepsy than in the general population. This is largely related to the etiology of the epilepsy and is probably not influenced by its treatment. On the other hand, most fatalities in patients with chronic, therapy-resistant epilepsy seem to be seizure related and are often sudden unexpected deaths (SUDEP). The frequency of such seizure-related deaths is most likely to be reduced by intensified treatment aimed at early seizure control, although appropriate studies for definitive evidence are still

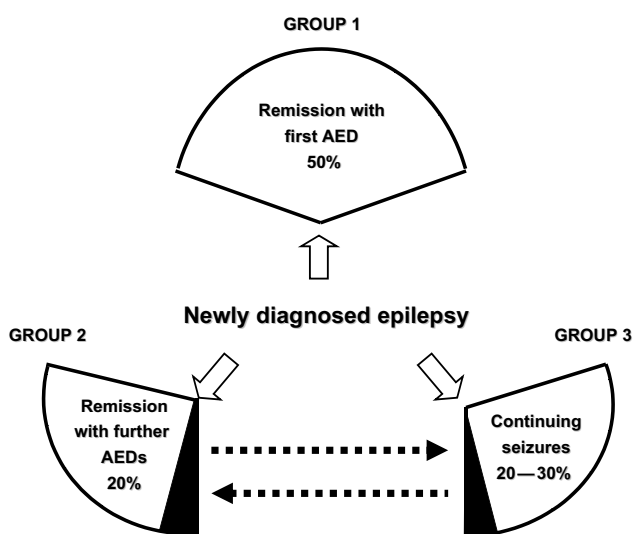


Fig. 6. Outcome of treatment of epilepsy.

lacking [for review, see 5]. Apparently, there is an increased rate of traffic accidents in drivers with epilepsy, even if population-based prospective data are lacking. Many of these accidents are seizure related.

*Recommendation.* *Epilepsy is a benign disorder for at least 50% of all patients. If the first AEDs do not lead to seizure freedom within a year, the future outlook is guarded and seizure control, if it occurs, as it does in 20–30% with a change of regimen, may take time, often several years. Uncontrolled epilepsy occurs in 36% and is associated with an increased risk of comorbidity, injury, and death.*

### 3. Drug treatment

The first 5 years of treating epilepsy in patients with new-onset epilepsy is crucial. The general treatment principles can be summarized in 11 points (Checklist 2.1). AEDs provide satisfactory control of seizures for most patients with epilepsy. About 65% of patients with new-onset epilepsy respond, seizure recurrence occurs in 5%, and 35% have uncontrolled epilepsy. The first AED controls seizures in 5 of 10 patients; in the other 5 patients, drug treatment fails because of poor efficacy in 2 patients, intolerable adverse events and idiosyncratic reactions in 2 patients, and other reasons for withdrawal (1 patient).

Modern AEDs are a diverse group of effective and safe drugs that have provided immeasurable benefits for those afflicted with seizure disorders of all kinds. Although the mechanism of action of antiepileptic drugs is of great scientific interest, our current failure to better understand the general mechanisms of seizure generation and of epileptogenesis, let alone those mechanisms operant in an individual patient, requires us to choose the best AED for an individual on clinical grounds. Pragmatically, the choice of the AED among first-line agents needs to be individualized based mainly on the patient profile, including the efficacy of the drug for the seizure or epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, includ-

ing the current or likely future need for concomitant medication for comorbidity, and finally cost (Fig. 7).

The following AEDs have been approved by regulatory agencies in the United States and Europe: acetazolamide, carbamazepine, clonazepam, clorazepate, ethosuximide, ethotoin, felbamate, gabapentin, lamotrigine, levetiracetam, mephenytoin, methsuximide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, trimethadione, valproate, vigabatrin, and zonisamide. The following additional agents are used mainly for the acute therapy of status epilepticus: diazepam, fosphenytoin, lorazepam, midazolam, and propofol.

*Recommendation.* *AEDs provide satisfactory control of seizures for most patients with epilepsy. About 65% of patients with new-onset epilepsy respond, seizure recurrence occurs in 5%, and 35% have uncontrolled epilepsy. Seizure precipitation can be avoided by lifestyle changes, particularly in adolescents. If two or three drug regimens have not brought complete seizure control, the diagnosis of epilepsy and of the epilepsy syndrome should be reevaluated, and if refractory epilepsy is confirmed, surgical options should be considered.*

#### 3.1. Starting treatment

The decision to start drug treatment in a patient with unquestionable epilepsy requires a careful individual risk–benefit assessment (Fig. 8). AEDs are able to prevent further seizures and reduce the severity of seizures, and treatment is recommended in all persons with a high risk of seizure recurrence. High-risk features are symptomatic epilepsy with GTC seizures, complex or simple partial seizures, and idiopathic generalized epilepsies. Early treatment after a first GTC seizure has, however, not been shown to improve the long-term prognosis or lower the mortality or risk of injury (Fig. 8) [17]. A number of patients with good prognosis (e.g., uncomplicated febrile seizures, often benign idiopathic partial epilepsies) may not even need drug treatment (see Section 2.9). Also,

#### Checklist 2.1

##### GENERAL TREATMENT PRINCIPLES

1. Treatment aims primarily to control seizures, and a return to health with a minimum of adverse events. Additional goals are social re-integration and preventing or reversing associated psychiatric complications.
2. The underlying causative disorder, if amenable, and comorbidity need to be treated as well.
3. A normal life with social activities should be encouraged including challenges that healthy persons face. A seizure provoking life style should be avoided, in particular excessive alcohol intake and sleep deprivation should be minimized. Cocaine and several other illicit drugs can trigger seizures. In case of fever continue drug treatment. Patients should self control drug compliance with a tablet dispenser.
5. Family members must be taught a commonsense attitude toward the patient. Overprotection should be replaced with sympathetic support that lessens feelings of inferiority and self-consciousness and other emotional handicaps.
6. Exercise is recommended; even such sports as swimming and horseback riding can be permitted when seizures are controlled.
7. Continued treatment with antiepileptic drugs is usually necessary.
8. No single drug controls all types of seizures, and different drugs are required for different patients. Patients rarely require several drugs.
9. Once seizures are controlled, the drug should be continued without interruption until at least 1–2 yr seizure-free.
10. Most licensing agencies permit automobile driving after seizures have stopped for 1 yr.
11. At that time, discontinuing the drug should be considered in patients with a low relapse risk.
12. If seizures cannot be controlled with drug treatment, however, surgical options including resection and vagus nerve stimulation should be considered early. Complacency should be avoided.



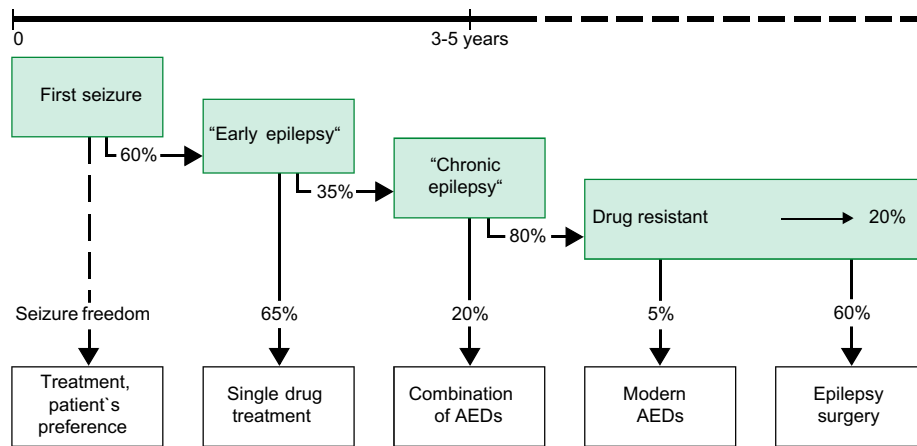


Fig. 7. Overview on management principles and estimates of seizure freedom after treatment in the first 3–5 years of new-onset epilepsy. Approximately 50% of patients become seizure free for 12 months with the first AED, if not, a change of medical regimen is achieving seizure freedom in another 20–30%. After failure of several AEDs, surgical options should be considered in suitable cases.

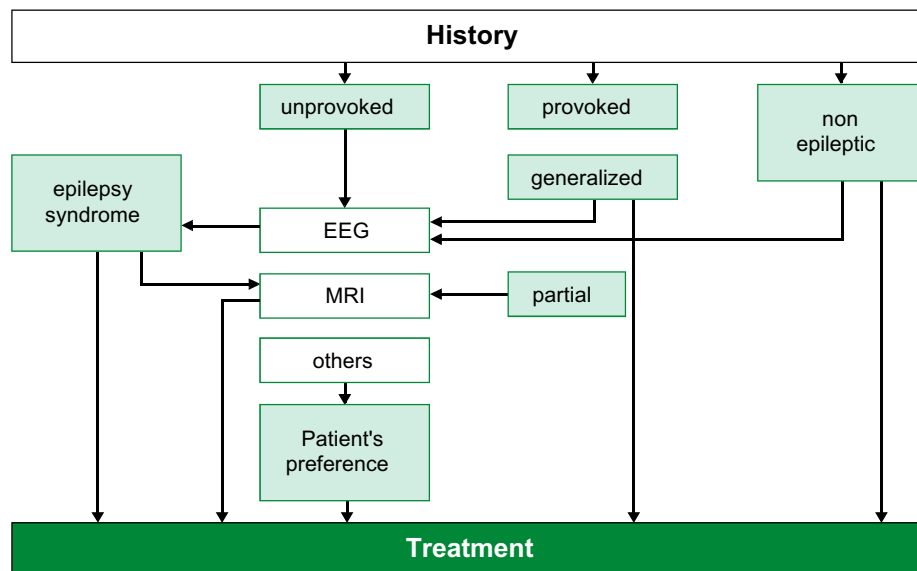


Fig. 8. Algorithm for starting drug treatment in a patient presenting with a first seizure. After a careful history, the clinical diagnosis of epilepsy is usually possible, if not, it may be prudent to observe another seizure before making a final diagnosis. In a patient with a first generalized tonic-clonic seizure, the decision to start an AED is usually based on the patient's preference after informed consent. If the diagnosis of an epilepsy syndrome can be made, as is often possible after review of the seizure and with the support of the EEG and the MRI, AED treatment is usually started, after informed consent.

adverse events of AEDs, including central nervous system toxicity and hypersensitivity reactions, have to be balanced against the potential benefit. Psychosocial consequences in case of another seizure (e.g., losing one's driver's license or an otherwise seizure-sensitive social setting) may weigh for drug treatment in some patients. Drug treatment is usually

not indicated if the diagnosis of epilepsy is uncertain, if provoked seizures occur that can be prevented without drugs, and, last not least, if the informed patient or caregiver does not want drug treatment (Checklist 2.2).

*Recommendation. Drug treatment of epilepsy is generally advisable if seizures are disabling or can be reasonably*

Checklist 2.2

STARTING TREATMENT

- Does the patient wish to be treated?
- Do you know your AED? (Test: Do you know the contraindications of the drug you wish to prescribe?)
- Have you given out a written scheme for dosing and drug titration?
- Does the patient have your emergency phone number?
- Don't promise too much, respect the known response to first AED

expected to recur sufficiently frequently to adversely affect the individual person more than the adverse effects of AEDs. The decision to start treatment after a single tonic–clonic seizure needs to be individualized because current AEDs prevent seizures in most patients but do not seem to affect the course of epilepsy.

### 3.2. Mechanism of drug action

AEDs prevent seizures by acting on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing is blocked without disturbing nonepileptic activity. However, the drugs have the remarkable ability to protect against seizures while permitting normal functioning of the nervous system. AEDs protect against seizures by a variety of different mechanisms (Table 4) [18].

In the end, AEDs are only a step on the way to the ultimate goal of epilepsy medicine, which is to provide treatments that prevent epilepsy or reverse it (Table 4). Although AEDs prevent seizures, they are not antiepileptogenic, able to prevent epilepsy or to affect the underlying tendency to generate seizures. *Antiepileptogenic* strategies are being developed using various animal models of

chronic epilepsy. By targeting plasticity mechanisms that underlie the enhanced seizure susceptibility that often follows brain insults such as head trauma, status epilepticus, and neonatal hypoxia, antiepileptogenic drugs of the future would prevent, or reverse, progressive worsening of the epileptic process.

*Recommendation.* Unfortunately, the mechanism underlying the therapeutic action of AEDs, although of great scientific interest and merit, is of little practical help in making a rational choice of AED, unless and until we better understand the mechanism of epilepsy and seizure generation for individual syndromes and patients.

### 3.3. Pharmacokinetics

From a clinical perspective, the ideal AED does not require monitoring of plasma concentrations, is metabolically inert, is not involved in drug interactions, and can be conveniently taken once or twice a day [19]. Unfortunately, a number of currently used classic AEDs induce or, less commonly, inhibit the cytochrome P450 system (carbamazepine, CBZ; phenobarbital, PHB; phenytoin, PHT) or inhibit enzymes involved in glucuronidation (valproate, VPA) (Table 5) [20]. Fortunately, modern AEDs

Table 4  
Antiepileptic drugs and their molecular targets<sup>a</sup>

Drug	Sodium channels	Calcium channels	GABA system	Glutamate receptors	Partial-onset seizure	Primary GTC seizure	Absence seizure	Myoclonic seizure	Infantile spasms	Lennox–Gastaut syndrome
Group A										
Phenytoin	+				+					
Carbamazepine	+				+					
Lamotrigine	+	HVA			+	+	(+)	+		
Zonisamide	+	T-type			+	+	(+)	(+)		(+)
Group B										
Phenobarbital		HVA	GABA <sub>A</sub> R	AMPA	+	+		+		
Benzodiazepines			GABA <sub>A</sub> R		+	+	+	+	(+)	(+)
Vigabatrin			GABA-T		+				+	(+)
Tiagabine			GABA transporter		+					
Ethosuximide	+	T-type					+	(+)		
Group C										
Gabapentin		HVA $\alpha\delta$	GABA turnover		+					
Pregabalin		HVA $\alpha\delta$	GABA turnover		+					
Levetiracetam		HVA			+	(+)	(+)	+		

Source. Modified from Ref. [18].

<sup>a</sup> It is convenient to categorize the actions of AEDs into those that involve (1) modulation of voltage-gated ion channels, (2) enhancement of synaptic inhibition, and (3) inhibition of synaptic excitation. Voltage-gated ion channels (including sodium, calcium, and potassium channels) shape the subthreshold electrical behavior of the neuron, allow it to fire action potentials, regulate its responsiveness to synaptic signals, contribute to the paroxysmal depolarization shift, and ultimately are integral to the generation of seizure discharges. In addition, voltage-gated ion channels are crucial elements in neurotransmitter release, which is required for synaptic transmission. Consequently, they are key targets for AEDs that inhibit epileptic bursting, synchronization, and seizure spread. Synaptic inhibition and excitation are mediated by neurotransmitter-regulated channels; these channels permit synchronization of neural ensembles and allow propagation of the abnormal discharge to local and distant sites. AEDs that modify excitatory and inhibitory neurotransmission, therefore, can also suppress bursting and, when they inhibit synaptic excitation, can have prominent effects on seizure spread. For convenience, three groups of compounds can be categorized according to their primary mechanisms. Group A: predominant sodium (and calcium) channel activity; Group B: GABA-mediated mechanisms; Group C: mixed, complex, or poorly understood actions. +, efficacy results from randomized controlled trials, several open studies, and generally accepted utility; (+), less extensive base of evidence.

Table 5  
Simplified synopsis of drug interaction properties of common AEDs

AED	Enzyme inducer (CYP) <sup>a</sup>	Enzyme inhibitor (CYP, UGT)	Effect of drug on disposition of other AEDs
Carbamazepine (CBZ)	Yes	No	LTG, TGB, VPA (▼▼)
Clobazam (CLB)	No	No	No relevant change
Ethosuximide (ETS)	No	No	PHT, VPA (▲), CBZ (▼)
Felbamate (FBM)	No	No	No relevant change
Gabapentin (GBP)	No	No	No relevant change
Lamotrigine (LTG)	Yes	Yes	No relevant change
Levetiracetam (LEV)	No	No	At OXC doses >900 mg (▼)
Oxcarbazepine (OXC)	Yes	No	CBZ, LTG, PHT, TGB, VPA (▼▼)
Phenobarbital (PHB)	Yes	No	CBZ, LTG, OXC, PHT, TGB, VPA (▼▼)
Phenytoin (PHT)	Yes	No	No relevant change
Pregabalin (PGN)	No	No	CBZ, LTG, PHT, TGB, VPA (▼▼)
Primidone (PRM)	Yes	No	No relevant change
Topiramate (TPM)	Yes (>200 mg/day)	No	No relevant change
Valproate (VPA)	No	Yes	PHT (▼), other AEDs (◄►)
Vigabatrin (VGB)	No	No	CBZ-E, LTG, PHB, free PHT (▲)
Zonisamide (ZNS)	No	No	No relevant change

Source. Modified from Ref. [20].

<sup>a</sup> CYP, cytochrome P450 system; UGT, uridine diphosphate glucuronyltransferase system; TGB, tiagabine; ◄►, no relevant change; ▼, increase in plasma concentration; ▼, decrease in plasma concentration; ▼▼, major decrease in plasma concentration.

are available that are less enzyme inducing (oxcarbazepine, OXC) or are not at all metabolized by the oxidative cytochrome P450 (gabapentin, GBP; lamotrigine, LTG; levetiracetam, LEV; pregabalin, PGN; or topiramate, TPM) and, therefore, are less likely to be involved in drug interactions (Table 5).

The absence of drug interactions is a very important advantage for an AED. Most patients with epilepsy are treated for several years, and a majority need AEDs for their lifetime. As a consequence, the long-term consequences need to be taken into account. For example, women might wish to take oral contraceptives at some periods in life; people become overweight or develop comorbid conditions such as depression, anxiety disorders, migraine, cardiovascular disease, diabetes, and cancer and may require additional medication. The increasing incidence of epilepsy in the elderly who commonly suffer from multimorbidity also require AEDs that do not interact. Finally, one in three patients with new-onset epilepsy will require a combination or a succession of AEDs over the life span for optimal seizure control. In addition, AEDs that interact with other drugs, for example, through enzyme induction or enzyme inhibition, will also disadvantageously affect the endogenous sexual and other hormone metabolism, and may contribute to adverse events. Taking enzyme-inducing CBZ, OXC, PHB, PHT, and primidone (PRM) may—in contrast to GBP, LEV and TPM at doses below 200 mg/day—lead to reduced efficacy of comedication including oral contraceptives and other AEDs. Adding an oral contraceptive may lower the plasma concentrations and efficacy of LTG, and vice versa. VPA does not interact with oral contraceptives, but may, however, inhibit glucuronidation of, for example, LTG. Fewer clinically relevant interactions with drugs or endogenous substances occur with OXC, TPM, and VPA instead of the classic enzyme-inducing AEDs, which are the least advantageous agents

in that respect. Finally, many classic AEDs share the disadvantage of both causing clinically relevant interactions and being affected by other drugs. For all these good reasons, the absence of enzyme induction or enzyme inhibition activity is a plus for any AED (Table 5).

Up to one in three patients with new-onset epilepsy require a combination of different AEDs for seizure control. In uncommon cases, even more than two AEDs may be needed. During combination therapy, a number of drug interactions may occur when classic AEDs are used. Drug interactions may interfere with drug efficacy. A prototypic example is the combination of CBZ and VPA. When VPA is added to CBZ, adequate VPA plasma concentrations cannot be achieved in most cases because CBZ lowers the plasma concentration of VPA. However, drug interactions may also increase the plasma concentrations to toxic plasma levels, for example, the increase in plasma concentration of LTG in the presence of VPA. Although this combination is beneficial for many patients, tremor may develop and the combination has been shown to be more teratogenic than LTG alone or in combination with another AED, except VPA. However, modern AEDs such as GBP, levetiracetam (LEV), PGN, and tiagabine (TGB) as are much better suited for combination therapy they are much less or not at all involved in drug interactions among AEDs (Table 5). By initiation of epilepsy treatment with modern noninteracting AEDs, such complications can be prevented.

A large number of patients with epilepsy rely on additional medication other than AEDs for birth control or management of disorders. Depression, anxiety disorders, and migraine are common in patients with epilepsy. Patients with epilepsy are not immune to development of such common diseases as stroke, myocardial infarction, and cancer, all of which require medication that may be interfered with by classic enzyme-inducing AEDs. Persons

Table 6  
Clinically relevant effect of AEDs on the disposition of other drugs

AED	▼ <sup>a</sup>	▲	Comments
Benzodiazepines	No relevant change	No relevant change	Higher sedation when taken with other sedating drugs (e.g., alcohol, PHB)
Carbamazepine	Anticoagulants, quinidine, contraceptives, corticosteroids, cyclosporine A, folate, digitalis glycosides, donezepil, doxycycline, felodipine, mebendazole, methadone, muscle relaxants, nifedipine, nimodipine, praxiquantel, theophylline, verapamil	Diltiazem	Lithium neurotoxicity may be functionally increased with comedication of AED. MAO inhibitors contraindicated
Felbamate	No relevant change	No relevant change	
Gabapentin	No relevant change	No relevant change	
Lamotrigine	Lower efficacy of oral contraceptives	Discontinuation of oral contraceptives may increase plasma concentration in some patients	Compromised efficacy of oral contraceptives has been reported in some patients
Levetiracetam	No relevant change	No relevant change	Partly metabolized by non-hepatic hydrolysis
Oxcarbazepine	Felodipine, contraceptives, nifedipine, nimodipine	No relevant change	Lithium neurotoxicity cannot be ruled out with comedication of OXC; MAO inhibitors contraindicated
Phenobarbital	Anticoagulants, quinidine, contraceptives, corticosteroids, cyclosporine A, diltiazem, digitalis glycosides, donezepil, doxycycline, felodipine, folate, griseofulvin, haloperidol, mebendazole, methadone, metoprolol, nifedipine, nimodipine, metronidazole, muscle relaxants, praxiquantel, propranolol, tacrolimus, tamoxifen, theophylline, verapamil	No relevant change	Methotrexate toxicity may be functionally increased with comedication of AED
Phenytoin	Anticoagulants, quinidine, contraceptives, corticosteroids, cyclosporine A, digitalis glycosides, donezepil, doxycycline, folate, mebendazole, methadone, muscle relaxants, nifedipine, nimodipine, praxiquantel, theophylline, verapamil	Diltiazem, disulfiram	Lithium neurotoxicity may be functionally increased with comedication of AED; MAO inhibitors contraindicated
Pregabalin	No relevant change	No relevant change	Pregabalin may cause peripheral edema. Exercise caution when co-administering pregabalin and thiazolidinedione antidiabetic agents
Primidone	See PHB	See PHB	
Tiagabine	No relevant change	No relevant change	
Topiramate	Contraceptives (TPM >200 mg/day),	No relevant change	
Vigabatrin	No relevant change	No relevant change	
Valproate	Itraconazole	Anticoagulants	VPA may functionally increase anticoagulation
Zonisamide	No relevant change	No relevant change	

Source. Modified from Refs. [19,20].

Abbreviations: See Table 5.

<sup>a</sup> ▼, Efficacy of specified drug may be lower with comedication of specified AED; ▲, toxicity of specified drug may be higher with comedication of specified AED; ◀▶, no relevant change in disposition.

with epilepsy may require antibiotics, which increase plasma concentrations of AEDs and may thus cause toxicity (Table 6). Starting treatment with modern noninteracting AEDs prevents such complications.

*Recommendation. Adverse drug interactions can be minimized by avoiding enzyme-inducing or -inhibiting classic AEDs and using beneficial combinations of AEDs, if needed for seizure control.*

### 3.4. Adverse effects

Possible adverse effects of AEDs are listed in Tables 7 and 8 [21,22]. The main advantages of some of the modern

AEDs include absence of hypersensitivity reactions, weight problems, and drug interactions that cause central nervous system toxicity. There is no need for routine laboratory monitoring and safety is improved without life-threatening organ damage. Patients receiving carbamazepine should have a complete blood count once a month for the first year of therapy. If the WBC or RBC count decreases significantly, the drug should be discontinued immediately. Patients receiving valproate should have liver function tests every 3 months for 1 year; if serum transaminase or ammonia levels increase significantly (to more than twice the upper limit of normal), the drug should be discontinued. An increase in ammonia up to 1.5 times the upper limit

Table 7  
Overview on adverse effects of AEDs<sup>a</sup>

	CBZ	CLB	ETS	FBM	GBP	LEV	LTG	OXC	PGN	PHB	PHT	TGB	TPM	VPA	VGB	ZNS
Early-onset adverse events																
Somnolence		++			+	+	+		+	++		++	++		+	++
Dizziness		++	+		+	+	+	++			++	++	++		+	+
Seizure aggravation	+	+			+				+		+	+			++	
Gastrointestinal	+		++	+	(+)	(+)		+						+		+
Liver failure				+										+		
Hypersensitivity (SJS/TEN)	+		+	+			+	+		+	+		+			+
Rash	+						+	+	+		+					
Late-onset adverse events																
Sedation		++	+							++			(+)			
Encephalopathy											+			+	++	
Depression			+							+	+	+			+	
Behavioral problems						+				++	+	+	++		++	+
Psychotic episodes	(+)		++	(+)	+	(+)				(+)	(+)	(+)	(+)	(+)	++	
Leukopenia	++		+	+				(+)		+	+					
Aplastic anemia	+		+	++						+	+					
Thrombopenia				+										++		
Megaloblastic anemia	(+)									+	+					
Pancreatitis					(+)									+		
Nephrolithiasis													(+)			+
Osteoporosis	(+)									+	+			(+)		
Hyponatremia	(+)							+								
Weight gain	+				+				++					+	+	+
Weight loss													+			
Cognition impaired	+	+								++	+		+			+
Teratogenicity														++		
Summary	9	8	10	7	5	3	4	6	4	14	13	7	9	9	12	9

Source. With data from Refs. [21,22].

<sup>a</sup> In general, although exposure to some modern AEDs is still limited, treatment with a number of modern AEDs appears to be advantageous compared with treatment with some of the classic AEDs (see summary of risks). It should, however, be noted that the incidence of many early adverse events shown here can be lowered by slow titration and avoiding above-average dosage and combination therapy, if possible. Teratogenicity is discussed in more detail in Table 8. (+), minimally increased risk in clinical use; +, risk higher than for AEDs without + sign; ++, highest risk among AEDs. For abbreviations of AEDs, see Table 5.

of normal can be tolerated safely. When an overdose reaction occurs, the amount of drug is reduced until the reac-

Table 8  
Major malformation rates after exposure to monotherapy of individual AEDs

n	Major malformations
No AED, n = 173	2.4% (0.9–6.0) <sup>a</sup>
Carbamazepine, n = 700	2.3% (1.4–3.7)
Valproate, n = 572	5.9% (4.8–8.2) <sup>b</sup>
Lamotrigine, n = 5390	2.1% (1.0–4.0)

Source. UK Registry: May 2003: 2637 completely documented pregnancies, total frequency of severe malformations = 4.1%.

<sup>a</sup> The 95% confidence interval is given in parentheses.  
<sup>b</sup> Significantly versus carbamazepine and lamotrigine [23]. No data are available on other AEDs from prospective studies. Fetal antiepileptic drug syndrome (abnormal facies, digital hypoplasia, microcephaly, and possibly developmental delay) occurs dose dependently in up to 4% of the children of epileptic women who take AEDs during pregnancy. Among commonly used drugs, carbamazepine and lamotrigine appear to be the least teratogenic; valproate may be the most teratogenic. There is suggestive evidence that malformations may be less frequent below a total daily dose of 1000 mg of valproate and 200 mg of lamotrigine [24]. Yet, because uncontrolled tonic-clonic seizures during pregnancy lead to fetal injury and death, continued AED treatment is generally advisable. For abbreviations, see Table 5.

tion subsides. When more serious acute poisoning occurs, the patient is given ipecac syrup or, if obtunded, is lavaged. After emesis or lavage, activated charcoal is administered, followed by a saline cathartic (e.g., magnesium citrate). Hemodialysis may be considered. The suspect drug should be discontinued, and a new AED started simultaneously. For more detailed discussion of adverse events, see [1].

*Recommendation. Adverse effects of AED treatment can be minimized by slow dose escalation up to average daily maintenance doses (unless increments are needed for seizure control), by avoidance of enzyme-inducing agents and polytherapy, if possible, and by use of appropriate well-tolerated modern AEDs for both new-onset and refractory epilepsy.*

### 3.5. Integrative choice of drug

Pragmatically, the choice of the AED among first-line agents needs to be individualized based mainly on the patient profile, including the efficacy for the seizure or epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, including the current or likely future need for concomitant medication for comorbidity, and finally cost (Checklist 2.3).

## Checklist 2.3

## Considerations on the choice of AED

All AEDs for a given class of seizures are similarly efficacious in percent of patients responding, however (unexplained) individual difference exist for individual response.

Chose the AED with the optimal risk-benefit profile for the individual patient

Ideally, the drug should be as efficacious as CBZ or VPA for the individual seizure or epilepsy, but better tolerated and safer (e.g., no increased teratogenicity compared to CBZ, no idiosyncratic reaction), should not be metabolized and have no or less enzyme induction properties compared to CBZ or show no or less enzyme inhibition compared to VPA.

\* The choice between numerous AEDs will be made after careful consideration of all other individual relevant factors (see checklist). In particular, suitable new AEDs which are less or not at all enzyme inducing, should be preferred over classic AEDs in adolescents and adults including women of childbearing age, patients with cognitive deficits or depression, with hormonal or metabolic disturbances, increased risk for osteoporosis, overweight, concomitant disorders or medication and the elderly.

### 3.5.1. Partial seizures

A number of AEDs are recommended based on their benefit–risk balance (Tables 9 and 10) [25,26]. The modern AEDs for therapy of previously untreated adolescents and adults with partial epilepsy, such as gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate, have a number of advantages compared with classic AEDs such as carbamazepine, phenobarbital, phenytoin, primidone, and valproate. The new AEDs are generally similar in efficacy, with the possible exception of gabapentin, which seems to be inferior in efficacy compared with CBZ, and are at least similar or better with respect to tolerability at adequate dosages than classic AEDs for patients with partial epilepsy. However, none of the modern AEDs evaluated in the SANAD trials was more efficacious than carbamazepine or valproate in their respective comparison groups [27,28]. Carbamazepine leads to complete seizure control in about 50% of patients; subsequent regimens with combination or substitution achieve control in up to 10–15%. One in three patients remains with uncontrolled partial seizures. In addition to the AEDs mentioned, efficacious second-line AEDs such as pregabalin and zonisamide are available for combination if the first drug fails to control seizures.

If several of these drugs individually or in combination have failed, surgery should be considered. Third-line agents are available: clobazam, phenobarbital, phenytoin, primidone, tiagabine. Less often used agents with either tolerability or safety problems or no Class I evidence of efficacy (acetazolamide, bromide, felbamate, sulthiame, vigabatrin) should be used as a last resort. Given the similar efficacy in control of partial seizures, the choice among first-line AEDs needs to be individualized based mainly on the patient profile, including the epilepsy syndrome, tolerability, gender issues, pharmacokinetics, current or likely future need for concomitant medication for comorbid conditions, and cost.

### 3.5.2. Generalized seizures

A number of AEDs are recommended based on their benefit–risk balance (Tables 9 and 10). Despite requiring different treatment strategies, typical absence seizures, juvenile myoclonic epilepsy, and related idiopathic generalized epilepsies are often erroneously grouped with partial and other epilepsies under the broad term *epilepsy*. Further-

more, antiepileptic drugs are tested and licensed mainly for partial epilepsies, and there may be inappropriate generalizations for their use in “epilepsy.” This is exemplified by gabapentin, carbamazepine, oxcarbazepine, and phenytoin, which induce myoclonic seizures, and vigabatrin and tiagabine, which induce absence seizures; they are contraindicated in the idiopathic generalized epilepsies, which constitute a large minority of epilepsy syndromes. Valproate is still the drug of first choice for patients with idiopathic and symptomatic generalized epilepsy despite its disadvantages, particularly weight gain and teratogenicity, because the efficacy of valproate is unsurpassed by any modern suitable AED such as lamotrigine or topiramate (Fig. 9) [28]. Although lamotrigine and topiramate are used for previously untreated adolescents and adults with generalized or unclassified epilepsies, the efficacy of lamotrigine is inferior to that of valproate, whereas topiramate is not inferior to valproate.

Absence seizures are fundamentally different from any other type of seizure and, therefore, unique in terms of pharmacological treatment. Typical absence seizures are often easy to diagnose and treat. Valproate, ethosuximide, and lamotrigine, alone or in combination, are first-line therapy. Valproate controls absences in 75% of patients and also GTC seizures (70%) and myoclonic jerks (75%); however, it may be undesirable for some women. Similarly, lamotrigine may control absence and GTC seizures in possibly 50 to 60% of patients, but may worsen myoclonic jerks; skin rashes are common. Ethosuximide controls 70% of absences, but it is unsuitable as monotherapy if other generalized seizures coexist. Combinations of any of these three drugs may be needed for resistant cases. Low dosages of lamotrigine added to valproic acid may have a dramatic beneficial effect. Clobazam, particularly in absence seizures with myoclonic components, and acetazolamide may be useful adjunctive drugs.

Generalized myoclonic seizures are different pharmacologically from absence seizures. Primidone and phenobarbital, which may be a last resort for treatment of refractory juvenile myoclonic epilepsy, are ineffective and may even worsen absence seizures. The epilepsy syndrome may also play a role. For example, lamotrigine, which is effective in children with typical absence seizures, may worsen myoclonic seizures in infants with severe myoclonic epilepsy. Children are in general more vulnerable. Controlled

Table 9  
Choice of antiepileptic drugs<sup>a</sup>

Antiepileptic drug	Absence, myoclonic seizures, PGTC	Partial, sec. GTC	Partial, children	Neither partial nor generalized seizures	Lennox–Gastaut syndrome	Most important benefit(s)	Most important disadvantage(s)
Clobazam	⊙ ⊙	⊙	⊙	⊙ ⊙	⊙ ⊙	Good transient adjunctive agent	Loss of efficacy (tolerance)
Carbamazepine		⊙ ⊙ ⊙	⊙			Unsurpassed efficacy: PS	Enzyme inducer, cognitive adverse events in the elderly
Ethosuximide	⊙ ⊙ ⊙ Absence only					Efficacy: absence	Rare: psychotic episodes, anorexia
Felbamate					⊙	Efficacy: drop attacks	Rare: aplastic anemia, liver failure; irritability
Gabapentin		⊙ ⊙	⊙ ⊙			Efficacy: PS, no drug interaction	High doses may be required
Lamotrigine	⊙ ⊙	⊙ ⊙ ⊙	⊙ ⊙	⊙ ⊙ ⊙	⊙ ⊙	Efficacy: PS, PGTC, absence, myoclonic, mood stabilizer	Slow titration, rash
Levetiracetam	⊙ ⊙	⊙ ⊙	⊙ ⊙	⊙ ⊙		Efficacy: PS, no titration, few drug interactions	Psychiatric abnormalities
Oxcarbazepine		⊙ ⊙ ⊙	⊙ ⊙			Efficacy: PS, fewer adverse events than CBZ	Rare symptomatic hyponatremia (caution: patients on diuretics)
Phenobarbital	⊙ ⊙ Myoclonic and PGTC only	⊙ ⊙, IV	⊙, IV			Efficacy: PS, PGTC, myoclonic, IV	Enzyme inducer, mental slowing
Phenytoin		⊙ ⊙ ⊙, IV	⊙, IV			Efficacy: PS, IV	Enzyme inducer, no dose-linear pharmacokinetics
Pregabalin		⊙ ⊙				Efficacy: PS, no drug interactions	Weight gain
Primidone	⊙ ⊙ Myoclonic and PGTC only	⊙ ⊙	⊙			Efficacy: PS, PGTC, myoclonic,	Enzyme inducer, mental slowing
Tiagabine		⊙		⊙		Efficacy: PS, PGTC, no drug interactions	Rare: may provoke absence status
Topiramate	⊙ ⊙ Myoclonic and PGTC only	⊙ ⊙ ⊙	⊙ ⊙ ⊙	⊙ ⊙ ⊙	⊙ ⊙	Efficacy: PS, PGTC, absence, myoclonic, weight reduction	Cognition including aphasic problems, rare: anorexia
Vigabatrin				⊙ ⊙ ⊙ IS only		Efficacy: PS, IS, no enzyme inducer	Irreversible visual field defects
Valproate	⊙ ⊙ ⊙, IV	⊙ ⊙, IV	⊙, IV	⊙ ⊙ ⊙, IV	⊙ ⊙ ⊙, IV	Efficacy: PS, PGTC, absence, myoclonic	Weight gain, teratogenicity
Zonisamide	⊙	⊙ ⊙		⊙		Efficacy: PS, PGTC, absence, myoclonic	Rare; nephrolithiasis

Source. Modified with data from Refs. [25,26].

<sup>a</sup> ⊙ ⊙ ⊙, First choice, class I or II evidence; ⊙ ⊙, second choice or adjunctive therapy, class I–III evidence; ⊙, third choice or adjunctive therapy, no class III or IV evidence. PGTC, primary generalized tonic–clonic seizure; sec. GTC, secondarily generalized tonic–clonic seizure; PS, partial seizures; IS, infantile spasms. Class I evidence comes from large randomized controlled trials (RCTs) comparing new drug with classic drug. Class II evidence comes from RCTs in smaller populations or well-designed retrospective control with classic drug. Class III evidence comes from retrospective blinded studies. Class IV evidence comes from open studies, expert opinion, or case reports with no controls. See specific product characteristics (SPC) for detailed individual drug profiles.

Table 10  
Preferred first-line AEDs for treatment of new-onset and refractory epilepsy in adults<sup>a</sup>

New-onset epilepsies	Refractory epilepsy
Partial epilepsies	
Carbamazepine	Pregabalin
Gabapentin	Zonisamide
Lamotrigine	Clobazam
Levetiracetam	
Oxcarbazepine	
Topiramate	
Valproate	
Idiopathic generalized epilepsies	
Lamotrigine	Clobazam
Topiramate	Levetiracetam
Valproate	

Source. Modified with data from Refs. [25,26].

<sup>a</sup> For refractory cases, all first-line AEDs for new-onset cases are also considered unless they have failed during previous treatment. The daily dosages for adults and children are given in Tables 13 and 14, respectively.

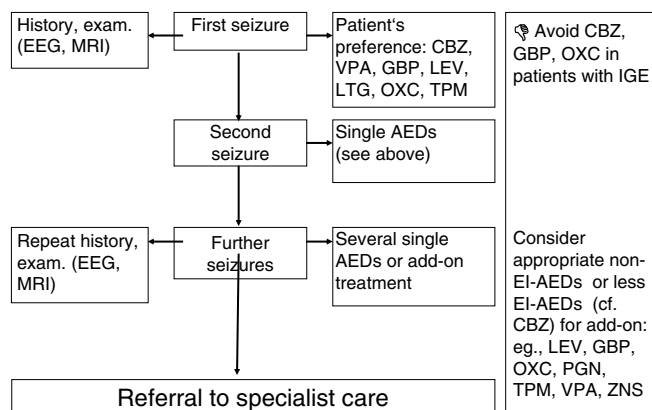


Fig. 9. Drug treatment algorithm. Abbreviations: Antiepileptic drugs, see Table 5, EI, enzyme-inducing; IGE, idiopathic generalized epilepsies.

studies of new AEDs in pediatric populations are significantly behind those for adults; consequently, such agents are initially licensed for adults only. Pediatricians have to learn by success or failure in daily practice.

### 3.5.3. Advantages of modern antiepileptic drugs

Most modern AEDs are less enzyme inducing than carbamazepine, phenytoin, or barbiturates or less enzyme inhibiting than valproate, or do not influence hepatic enzyme systems at all. This is why, in general, treatment with modern AEDs results in fewer adverse drug interactions. During long-term exposure to some of the newer AEDs, one can reasonably expect fewer hormonal/metabolic disturbances. Based on current evidence, the rate of major malformations associated with the use of lamotrigine is similar to that for carbamazepine treatment or for untreated women with epilepsy and is lower than that observed with valproate treatment. A second very important advantage of some of the modern AEDs is the absence of hypersensitivity reactions (see Table 7). These data sug-

gest, in our view, that a modern AED should be preferred over a classic AED when starting drug treatment in a patient with new-onset epilepsy (Table 10). In addition, the choice of an AED is also influenced by the individual patient's characteristics (Table 11). When first-line AEDs produce insufficient results, a number of second- and third-line AEDs are available. As these drugs all have quite significant limitations with respect to evidence of efficacy or, at least in part, safety concerns (see adverse effects), they are recommended only in cases of disabling refractory epilepsy (Table 12).

*Recommendation.* The choice among first-line AEDs needs to be individualized based mainly on the patient profile including the efficacy for the seizure or epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics, current or likely future need for concomitant medication for comorbidity, and finally cost and physician preference. In our view, a suitable modern AED should be preferred over a classic AED for treatment of partial seizures.

### 3.6. Finding the optimal dose

The drug of choice for the particular type of epilepsy is started at the lowest effective dose. If seizures continue, the daily dose is increased by small increments to the average effective dose (Table 13) [25,26]. Except in an emergency, there is no need for rapid titration. Most modern AEDs work within several days to a week of starting treatment. Rapid titration is not only unnecessary, but may even be harmful. It increases the risk of cutaneous hypersensitivity reactions, for example, with carbamazepine, lamotrigine, and phenytoin, and adds to the risk of avoidable central nervous system toxicity, particularly during early primidone therapy. It was found in recent years that the average effective dose achieves seizure control in about 70–80% of those who respond at all doses, including above-average doses. As a consequence, in those who are not controlled by a well-tolerated average dose, a dose increment may be useful, but only for about 20–30% [29]. If seizure control cannot be achieved with the maximum tolerated dose, reduction to the previous average dose is recommended. If toxic symptoms or high plasma concentrations indicating an increased risk of toxicity develop before seizures are controlled, a second AED is added, again guarding against toxicity. Interactions between the drugs can interfere with their rates of metabolic degradation. When a patient does not respond sufficiently, gradual withdrawal from the initial, failed AED and a switch to monotherapy with the recently added AED is an option. If the patient responds well, a combination of both drugs is usually maintained unless side effects require downtitration to lower the total drug load. Daily dosages for adults and children are summarized in Tables 13 and 14. The time to reach average daily dosages varies considerably among AEDs (Table 13).

Patients with renal or hepatic disorders may require dose adjustments. Dose of gabapentin, pregabalin, leveti-



Table 11  
Choice of AEDs to consider for different patient profiles, if possible<sup>a</sup>

Feature	Consideration
Efficacy for individual seizure and epilepsy syndrome	Prefer efficacious first-line agents (I)
Tolerability of AED? Any issues to be discussed	Prefer well tolerated first-line agents (I)
Older than 65 years	Prefer GBP or LTG over CBZ (I)
Male hypogonadism	Prefer GBP, LTG, OXC, and TPM over enzyme-inducing AEDs such as CBZ (III)
Body mass index > 25 kg/m <sup>2</sup>	Prefer weight-neutral AEDs such as CBZ, LTG, and OXC over VPA, GBP, or PGN, or prefer TPM for weight loss (III)
Depression	Prefer CBZ, GBP, LTG, VPA, and TPM over PHT, PHB, or VGB (III)
Anxiety	Prefer GBP and PGB over LEV, PHT, PHB, or VGB (III)
Mood disorders	Prefer CBZ, GBP, LTG, VPA, and TPM over PHT, PHB, or VGB (III)
Cognition issues	Prefer CBZ, GBP, LTG, VPA, and OXC over PHB or PRM (III)
Lipid profile	Prefer OXC and TPM over CBZ (III)
Osteoporosis	Prefer GBP, LTG, and OXC over enzyme-inducing AEDs such as CBZ and VPA, which may activate osteoclastic activity
Current or future comedication	Prefer non-enzyme-inducing agents (III)
History of idiosyncratic reactions	Prefer AEDs that do not cause such reactions, such as GBP (I)

<sup>a</sup> Evidence class in parentheses. For abbreviations of AEDs, see Table 5.

Table 12  
Choice of second- and third-line AEDs, mainly for refractory epilepsy<sup>a</sup>

AED	Partial adjunctive therapy, adult	Partial monotherapy	Partial, children	Primary generalized	Symptomatic generalized (Lennox–Gastaut syndrome)
Acetazolamide	No	No	No	No	No
ACTH and steroids	No	No	No	No	No
Benzodiazepines	Yes	No	Yes	Yes	No
Bromide	No	No	No	No	No
Ethosuximide	No	No	No	Yes (absence) No (myoclonic)	No
Felbamate	Yes	Yes	Yes	No	No
Primidone	Yes	Yes	Yes	Yes (myoclonic) No (absence)	No
Sulthiame	No	No	Yes	No	No
Tiagabine	Yes	No	No	No	No
Vigabatrin	Yes	No	No	No	No

Source. Modified with data from Refs. [25,26]

<sup>a</sup> Yes = Class I/II evidence, No = insufficient evidence exists to recommend use, although class III/IV may exist. The most effective AEDs for long-term use and their doses are given in Tables 13 and 14.

racetam, vigabatrin and zonisamide, which are excreted renally, should be lower in patients with reduced renal function (for details see US package insert or EMEA SPC). Dose of AEDs such as benzodiazepines, carbamazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate and valproate, which are primarily metabolized hepatically, should be reduced in patients with hepatic insufficiency (for details see US package insert or EMEA SPC). Monitoring of serum concentrations and careful titration to the lowest dose needed for seizure control are recommended.

*Recommendation. Slow titration up to average maintenance doses is generally advisable, because rapid dose escalation and higher-than-average dosages cause unnecessary adverse events. Higher-than-average doses improve seizure control in only an additional 20–30% of all responders. If the therapeutic benefit is not realized after further dose esca-*

*lation, a return to the previous dose will avoid unnecessary toxicity.*

### 3.7. Single-drug versus add-on therapy

When single-drug therapy is not able to control seizures, adding a second drug and substitution monotherapy are common options. When the initially prescribed AED fails to produce seizure freedom, transfer to monotherapy with an alternative agent (substitution) will lead to seizure control in as many as 15–30% of cases [29,30]. Two randomized controlled trials with mostly old, enzyme-inducing AEDs have compared substitution with combination therapy and demonstrated rather similar outcomes [31,32]. Based on the available evidence, there are no conclusive data favoring either substitution monotherapy or add-on treatment. Except for patients with severe idiosyncratic reactions, where substitution is clearly preferable, a prag-

Table 13  
Dosages and effective plasma concentrations of often-used AEDs for adults

AED	Suggested titration	Suggested average target dose (mg/day)	Time to reach average dose (weeks)	Target plasma concentration (mg/L)
Carbamazepine	200 mg every 3 days	600–1200, bid or tid	≤3	3–12
Clobazam	10 mg/day	10–20, bid	≤1	<sup>a</sup>
Felbamate	300 mg every 7 days	2400–3600, bid, tid,	≤6	20–45
Gabapentin <sup>b</sup>	300 mg every 1–3 days	900–2400, bid, tid	≤3	<sup>a</sup>
Lamotrigine	Monotherapy: 25 mg for 2 weeks, 50 mg for the next 2 weeks, then increases of 50–100 mg/week. Add-on in the presence of VPA: 25 mg every other day for 2 weeks, 25 mg/day for next 2 weeks, then increases of 25–50 mg/week. Add-on in the presence of enzyme-inducing AEDs: 50 mg for 2 weeks, 100 mg for the next 2 weeks, then increases of 50–100 mg/week	100–400 qd, bid	≤7–10	2–15
Levetiracetam <sup>b</sup>	500 mg every 1–3 days	1000–3000, bid	≤2	<sup>a</sup>
Oxcarbazepine	150 mg every 3–7 days	800–1800, bid, tid	≤2–3	7.5–20 (MHD)
Phenobarbital	50 mg every 7 days	50–200, qd, bid	≤4	10–40
Phenytoin	50–100 mg every 3–5 days, beyond 200 mg in 25-mg steps	200–300, bid, tid	≤2	5–25
Pregabalin <sup>b</sup>	75–150 mg every 3–7 days	150–600	≤4	<sup>a</sup>
Primidone	62.5–250 mg every 7 days	500–750, tid	≤8	10–40 (PHB)
Tiagabine	6 mg every 5–7 days	36–60, tid	≤5	<sup>a</sup>
Topiramate	25 mg for 1–2 weeks; beyond 100 mg, 25–50 mg/week	100–400, bid	≤4–6	<sup>a</sup>
Vigabatrin <sup>b</sup>	500 mg every 7 days	500–3000, bid	≤2	<sup>a</sup>
Valproate	500 mg every 3–7 days	600–1500, bid slow release, tid	≤2	40–120
Zonisamide <sup>b</sup>	25 mg	300	≤3	

<sup>a</sup> Irrelevant.

<sup>b</sup> Dose should be lower in patients with reduced renal function (for details see US package insert or EMEA SPC).

matic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug. This may prevent the substitution of a partially efficacious drug with a nonefficacious drug. Reduction of the first drug prevents unnecessary drug exposure in the case of adverse effects. The choice of the second drug should be based on which first drug failed. The use of newer-generation AEDs that are not involved in drug interactions may provide a better outcome for add-on treatment, which is more vulnerable to adverse drug interactions than substitution monotherapy. The main advantages of substitution monotherapy compared with combination therapy include simplicity, allowing clear attribution of the observed clinical effect; no unnecessary drug load (overtreatment) as in combination therapy; no detrimental drug interactions; and no adverse effects of specific combinations, for example, increased teratogenicity with a combination of valproate and lamotrigine. Furthermore, transfer to monotherapy has been shown to be useful when combination therapy has failed to provide sufficient seizure control. A safe and well-communicated transfer schedule is as essential as the choice of optimal agent for the success of either combination or substitution therapy.

*Recommendation.* Except for patients with severe idiosyncratic reactions, for whom substitution is clearly preferable, a pragmatic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug if the response to the combination is not impressive. Combining

may prevent the substitution of an insufficiently efficacious drug with a nonefficacious drug. Reduction of the first drug prevents unnecessary drug exposure in the case of adverse effects. With respect to the choice of the next drug, all drugs that have failed in the past should be avoided and modern AEDs, which are better suited for combination therapy because of their lack of adverse drug interactions, should be considered.

### 3.8. Monitoring treatment

Target plasma AED concentrations are available for a number of drugs (see Table 13). However, plasma AED concentrations are less useful to follow than the clinical course. Some patients have toxic symptoms at low concentrations, whereas others tolerate higher concentrations without apparent clinical symptoms. Some patients respond at very low concentrations, and others do not respond even to very high concentrations. If treatment is ineffective, monitoring of concentrations may unmask irregular drug compliance; conversely, high plasma concentrations may indicate increasing to a higher dose is not likely to lead to a better response and, in addition, involves a higher risk of drug toxicity. In a patient with unexplained central nervous system toxicity, high plasma AED concentrations may be useful for the diagnosis and management of the intoxication. Except for phenytoin, for which monitoring is strongly recommended, particu-

Table 14  
Dosages of AEDs for children<sup>a</sup>

AED	Daily dosage and titration
Bromide	300-mg starting dose, average dose (mg/day) up to 2100 mg; time to reach average dose is 8 weeks
Acetazolamide	8–30 mg/kg in daily divided doses, not to exceed 750 mg/day
Carbamazepine	<6 years: initially 5 mg/kg, divided bid, tid, qid; increased every 5–7 days up to 20 mg/kg 6–12 years: initially 10 mg/kg bid; maximum 200 mg; increased by 100 mg/day at weekly intervals up to 15–30 mg/kg
Clonazepam	Initially 0.01–0.03 mg/kg; maximum 0.05 mg/kg bid, tid; increased by 0.25–0.5 mg/kg every 3 days until seizures are controlled or adverse effects occur; for maintenance, 0.1–0.2 mg/kg tid
Ethosuximide	<6 years: initially 15 mg/kg divided bid, maximum 500 mg; increased every 4–7 days; for maintenance 15–40 mg/kg bid, maximum 1500 mg >6 years: initially 250 mg bid; increased by 250 mg bid as needed every 4–7 days; for maintenance, usually 20–40 mg/kg bid, maximum 1500 mg
Felbamate	4–14 years: start with 7.5–15 mg/kg per day bid or tid; lower dose of phenytoin or valproate comedication by 20–30%; increase the dose by 7.5 mg/kg per day every 2 weeks, if needed; do not exceed total daily dose of 45 mg/kg or 3600 mg
Gabapentin	10–50 mg/kg tid, qid
Lamotrigine	<12 years, add-on with enzyme-inducing AED, no VPA: initially 0.6 mg/kg/day for 2 weeks, then 1.2 mg/kg/day for 2 weeks; maximum 15 mg/kg/day or 400 mg/day <12 years, add-on with enzyme inducing AED and VPA: initially 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, then 1.2 mg/kg/day in 1 or 2 doses; maximum 5 mg/kg/day or 200 mg/day <12 years, add-on with VPA, no enzyme-inducing AEDs: initially 0.15 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day; maximum 5 mg/kg/day or 200 mg/day
Levetiracetam	4–11 years and adolescents (12–17 years) weighing less than 50 kg: initial therapeutic dose 10 mg/kg bid; dose can be increased to 30 mg/kg bid; dose changes should not exceed 10 mg/kg every 2 weeks. Children 20 kg or less should preferably start the treatment with 100 mg/ml oral solution. The starting dose of 10 mg/kg daily corresponds to 150 mg, 200 mg, and 250 mg bid for children with a weight of 15 kg, 20 kg, and 25 kg, respectively. The maximum dose of 30 mg/kg bid translates to 450 mg, 600 mg and 750 mg bid for children with a weight of 15 kg, 20 kg, and 25 kg, respectively. Dosage in children 50 kg or greater is the same as in adults.
Oxcarbazepine	<6 years: 1-month to 4 years of age: start with 8–10 mg/kg body weight, increase by no more than 10 mg/kg per week, up to a maximum dose of 60 mg/kg, if needed. In children aged 1 month to 4 years, the daily dose is about twice as high as in adults, in children aged 4–6 years, the daily dose is 50% higher as in adults. ≥6 years: initially 8–10 mg/kg/day, increased every week by 10 mg/kg/day; maximum 46 mg/kg/day given bid
Phenobarbital	Neonates: 3–4 mg/kg, then increased Infants: 5–6 mg/kg in one or two divided doses
Phenytoin	Neonates: initially 5 mg/kg bid; for maintenance, usually 5–8 mg/kg bid, tid
Pregabalin	Use in patients under 17 years is not recommended (EMA SPC).
Primidone	<8 years: initially 50–125 mg at bedtime; increased by 50–125 mg/day every 3–7 days; for maintenance, usually 10–25 mg/kg divided tid or qid
Tiagabine	Use in patients under 12 years is not recommended.
Topiramate	Initially 0.5–1 mg/kg; increased 0.5–1 mg/kg bid weekly or biweekly; for maintenance, usually 3–6 mg/kg in monotherapy, 5–9 mg/kg in combination, bid
Vigabatrin	Monotherapy for treatment of West syndrome: start with 50 mg/kg/day, doses ≤150 mg/kg/day have been tolerated
Valproate	Initially 10–15 mg/kg bid, tid; increased by 5–10 mg/kg/day at weekly intervals; for maintenance, usually 30–60 mg/kg bid, tid
Zonisamide	Use in patients under 18 years is not recommended (EMA SPC).

<sup>a</sup> For target plasma concentrations, see Table 13.

larly at concentrations greater than 20 mg/L, because of its nonlinear saturation dose kinetics, monitoring of other AED plasma concentrations is optional and should be individualized.

*Recommendation.* Except for phenytoin, for which monitoring is strongly recommended, particularly at concentrations above 20 mg/L, because of its nonlinear saturation dose kinetics, monitoring of other AED plasma concentrations is optional and should be individualized (e.g., poor drug compliance or adverse events).

### 3.9. Drug-resistant epilepsy

The definition of drug resistance is elusive. In the broadest sense, all epilepsy is drug resistant, because drugs are a palliative treatment preventing the clinical expression of seizures but cannot affect the underlying pathological state. In a large study of patients evaluated and treated in Glasgow, Scotland, Kwan and Brodie [33] found that of 470 patients who had never before received an AED, 301 (64%) became seizure free for at least 12 months during treatment. Of these patients, 113 discontinued the first drug because of lack of efficacy, 69 because of intolerable side effects, 29 because of idiosyncratic reactions, and 37 for other reasons. Only 79 of these 248 patients (32%) subsequently became seizure free. The outcome among these patients was strongly associated with the reason for the failure of the first drug. Another 12 (11%) of the patients in whom treatment with the first drug was ineffective subsequently became seizure free. Only 4% adequately responded to a third drug. Similarly, only 3% of patients responded to two drugs. However, new evidence from several studies has suggested that Kwan and Brodie's results may have been too pessimistic. Long-term observations indicate that as many 20–30% with apparent drug-resistant seizures will eventually enter remission after a change in drug regimen [e.g., 34,35]. The good outcome in as many as one of five patients indicates that there is hope even after many years of having uncontrolled epilepsy.

If epilepsy is considered drug resistant if treatment fails to achieve seizure freedom for 12 months or more, for whatever reason, as many as 36% of newly treated patients are drug resistant [33]. However, if the definition of frequent and severe seizures despite optimal treatment is used so that alternative therapies including surgery might be indicated, only 5–10% of newly diagnosed patients are estimated to be drug resistant [36]. The definition proposed by Berg [37] of intractable epilepsy as failure of two or more drugs and occurrence of one or more seizures per month over 18 months appears reasonable.

There are multiple reasons why patients may be resistant to AED therapy. An incorrect diagnosis may lead to ineffective treatment. For example, use of carbamazepine in a patient with absence seizures and generalized spike wave activity could exacerbate seizures. Likewise, treating a patient with complex partial seizures with ethosux-

imide is unlikely to be helpful. Certain AEDs such as gabapentin, pregabalin, vigabatrin, and lamotrigine can exacerbate myoclonic seizures. It has been suggested that altered drug permeability across the blood–brain barrier may be involved in pharmacoresistance to AEDs. ATP-dependent multidrug transporters such as P-glycoprotein are found in the luminal membranes of brain capillary endothelial cells and are known to play a role in blood–brain barrier function by limiting drug penetration into the brain. Reduced target sensitivity of use-dependent blockade of voltage-dependent Na<sup>+</sup> channels in carbamazepine-resistant patients is another novel mechanism underlying the development of drug-resistant epilepsy. It is now clear that although the new-generation AEDs are very useful, they are not able to reverse drug-resistant epilepsy in the vast majority of patients [38]. The medical, social, and economic consequences of poorly controlled seizures can be enormous. Recurrent seizures are associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Frequent seizures not only influence quality of life, morbidity and mortality in epilepsy, but also significantly increase costs.

*Recommendation.* Although the exact mechanism(s) of drug resistance remains elusive, we know that a change in regimen in apparently refractory epilepsy will eventually lead to seizure freedom in as many as one in five patients. Avoiding resignation on the side of the patient and complacency on the side of the physician is essential for the success of medical treatment. Drug-resistant epilepsy is associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Early referral for exploring surgical treatment is advisable; two-thirds of patients respond to AEDs after surgery, and one-third will remain seizure free after AEDs have been withdrawn. If surgery is not an option, a change in medical regimens and palliative vagus nerve stimulation are good options.

### 3.10. Limitations of current treatment

#### 3.10.1. Prophylactic treatment

Head injuries with skull fractures, intracranial hemorrhages, focal neurological deficits, or amnesia cause post-traumatic epilepsy in 25 to 75% of cases. Prophylactic treatment with anticonvulsant drugs after the head injury reduces the probability of early posttraumatic seizures during the first few weeks after the injury, but does not prevent the development of permanent posttraumatic epilepsy months or years later. Early treatment after a second tonic–clonic seizure does not improve the long-term outcome of the epilepsy. It is now clear that although the new generation of AEDs is very useful, many patients in whom previous drug regimens were ineffective will not respond to the drugs. A challenge for the scientific community is to determine the causes for these drug failures and circumvent obstacles to seizure control by developing novel treatment strategies.

### 3.10.2. Seizure aggravation

Seizure aggravation is an important limitation of current AEDs. Idiopathic generalized epilepsies are particularly prone to pharmacodynamic aggravation: typical absence seizures are consistently increased by carbamazepine, vigabatrin, tiagabine, and gabapentin, whereas phenytoin is less aggravating. Juvenile myoclonic epilepsy is often aggravated by carbamazepine and, less consistently, by phenytoin and other AEDs. The GTC seizures experienced in idiopathic generalized epilepsies may respond to AEDs that aggravate other seizure types. Nonconvulsive status epilepticus has been associated with tiagabine. Gabapentin-associated myoclonus appears to occur relatively frequently. It is usually mild and can easily be overlooked. Discontinuation of therapy is not necessary in most cases. In symptomatic generalized epilepsies, patients often experience several types of seizures that respond differently to AEDs: myoclonias are generally aggravated by the same drugs that aggravate idiopathic generalized epilepsies; tonic seizures in the Lennox–Gastaut syndrome respond to carbamazepine, which may, however, aggravate atypical absences. In severe myoclonic epilepsy of infancy, lamotrigine has a nearly consistent aggravating effect. In some patients with benign Rolandic epilepsy, a clear aggravation may be produced by carbamazepine, with occurrence of negative myoclonias, atypical absences, drop attacks, and, at the maximum, evolution into a state of electrical status epilepticus during sleep. Only a few medications can control idiopathic generalized epilepsies without potentially causing seizure aggravation. Broad-spectrum antiepileptic drugs such as valproate, lamotrigine, and topiramate are extremely effective at controlling a variety of seizures without causing excessive seizure aggravation. Among these drugs, valproate has the longest clinical experience history and the largest body of published data.

*Recommendation.* Although AED treatment is beneficial for most patients, AEDs do not prevent epilepsy in persons at risk or drug-resistant epilepsy even when given early. Aggravation of mostly myoclonic or absence seizures by drugs used to treat partial seizures is another problem.

### 3.11. Emergency treatment

#### 3.11.1. Single seizure

A single seizure, which usually lasts no longer than 1–2 minutes, requires no emergency antiepileptic drug treatment. It will stop soon, whether or not treated. It is better to avoid seizure-induced injury by placing a blanket or a pillow under the head or pulling the patient away from fire or other risks of injury. During a seizure, injury should be prevented. Protecting the tongue should not be attempted because teeth may be damaged. Inserting a finger to straighten the tongue is dangerous and unnecessary. Clothing around the neck should be loosened. The patient should be rolled onto his or her side to prevent aspiration. A responsible fellow worker may be trained to give emergency aid if the patient agrees. In acute GTC seizures due

to febrile illness, ingestion of alcohol or other toxins, or acute metabolic disturbance, the causative condition must be treated as well as the seizures. Antiepileptic drugs are of little value in preventing alcohol withdrawal seizures. If only one seizure has occurred, a decision concerning long-term therapy must be made. However, patients with a series of several seizures or status epilepticus do require immediate emergency treatment.

#### 3.11.2. Status epilepticus

All types of repeatedly or continuously occurring epileptic seizures that in total last longer than 5–10 minutes (duration is controversial) require immediate treatment (Fig. 10, Checklist 2.4).

*Recommendation.* It is advisable to refrain from invasive drug treatment for single seizures or when there is doubt epilepsy is the diagnosis. However, when the diagnosis of a series of seizures or status epilepticus is certain, immediate and high-dose emergency treatment should be implemented according to a previously agreed on written schedule. Psychogenic nonepileptic status should be considered in cases of failure to control grand mal status after routine therapy with benzodiazepine plus phenytoin or valproate, before pursuing more aggressive treatment.

### 3.12. Avoidable treatment errors

#### 3.12.1. Overtreatment

The most common avoidable treatment errors stem from misdiagnosis and inadvertent overtreatment. Common forms of misdiagnosis occur early in the management of a patient who is thought to suffer from epilepsy but in fact has syncope with myoclonia or psychogenic nonepileptic seizures. Subsequent AED use provides no benefit, even at higher doses, which invariably result in adverse events. Overtreatment may, however, also occur in patients with unequivocal epileptic seizures. Although complete seizure control is the ultimate goal of pharmacological therapy, it should not be sought at all costs, and no patient with epilepsy should suffer more from the side effects of treatment than from the consequences of the underlying disease. Overtreatment is not uncommon in patients taking AEDs, and it may occur in many forms and with a variety of mechanisms. Long-term use (or continuation) of antiepileptic drug therapy in situations where it is not indicated (e.g., in children with simple febrile seizures or in seizure-free patients who have undergone brain surgery) constitutes an overt case of overtreatment. Other forms of overtreatment include the use of unnecessarily fast dose escalation rates, which may expose the patient to potentially serious or severe side effects, or the prescription of unnecessarily high maintenance dosages. The latter may result from an inadequate understanding of dose–response relationships, from misinterpretation of serum drug concentrations (e.g., targeting concentrations within the “range” in patients who are well controlled at lower concentrations), or, less often, from failure to recognize a par-

Status epilepticus

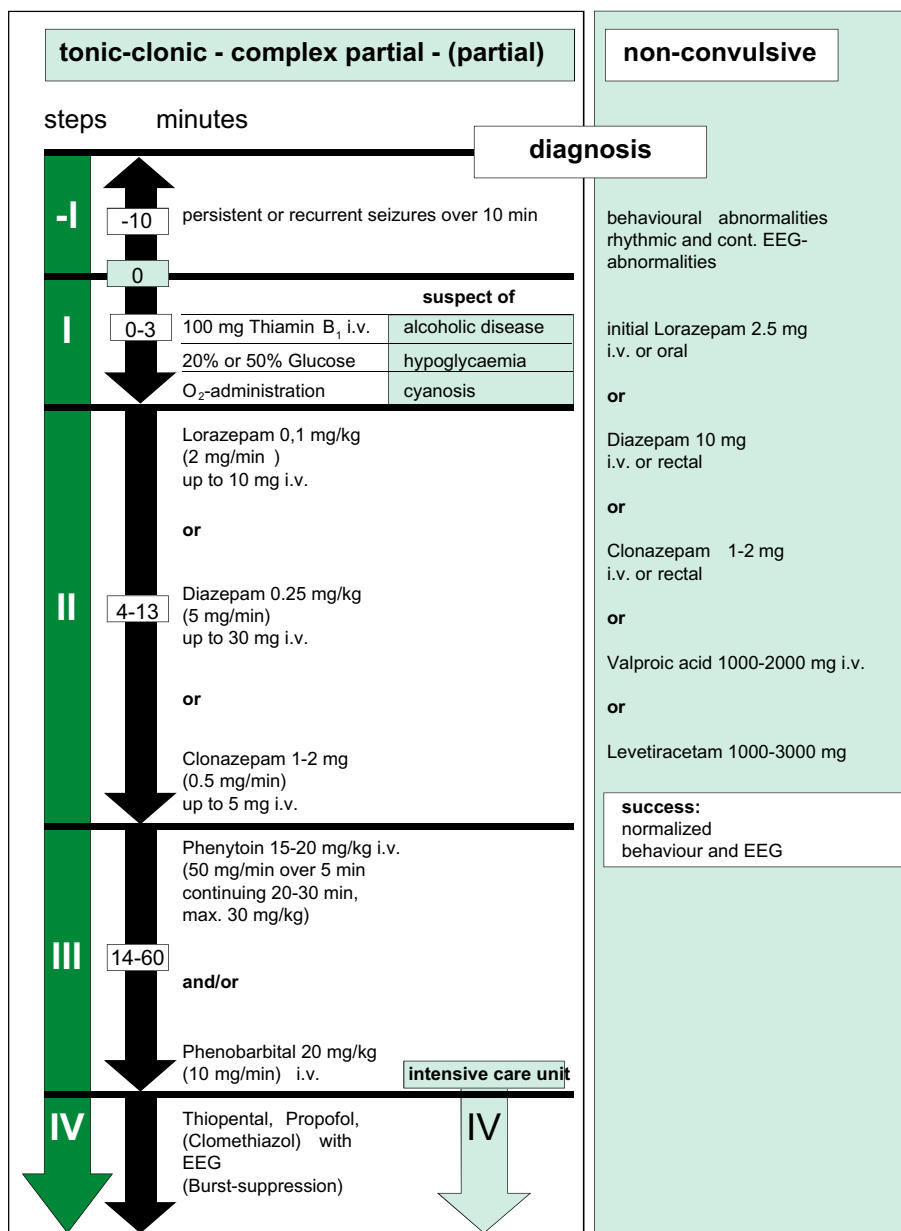


Fig. 10. Treatment of status epilepticus.

adoxical increase in seizure frequency as a sign of drug toxicity. The most common form of overtreatment, however, involves the unnecessary use of combination therapy (polypharmacy) in patients who could be treated optimally with a single drug. Adverse effects associated with polypharmacy often result from undesirable drug–drug interactions. Although pharmacokinetic interactions are somewhat predictable and can be minimized or controlled by serum drug concentration monitoring and/or dose adjustment, pharmacodynamic interactions leading to enhanced neurotoxicity (as seen, e.g., in some patients given a combination of lamotrigine and carbamazepine) can be identified only by careful clinical observation. There is evidence that not all AED combinations are equally

adverse, and that the combined use of specific drugs (e.g., lamotrigine and valproic acid) may even elicit an improved therapeutic index in some patients compared with either agent given alone, provided appropriate dose adjustments are made. In women of childbearing potential, however, the same combination is associated more often with fetal malformations than either drug alone. Unless and until we better understand the complexities of drug combinations, single-drug therapy may avoid inadvertent overtreatment associated with polypharmacy.

3.12.2. Undertreatment

Unfortunately, treatment of patients with uncontrolled epilepsy with suboptimal doses may prevent seizure remis-

## Checklist 2.4

## Management of status epilepticus

## Diagnostic Strategy:

According to observed predominant seizure type, status epilepticus falls in four clinical categories:

- A. Status of tonic-clonic seizures (convulsive status epilepticus, grand mal status).
- B. Non-convulsive status of complex partial seizures (psychomotor status)
- C. Non-convulsive status of generalized absence (petit mal or absence status) or myoclonic seizures. Look for paroxysmal, mostly spike wave, activity in the EEG, consider postictal confusion, dehydration, substance abuse for differential diagnosis.
- D. Other epileptic seizure types e.g., tonic, simple partial (uncommon)
- E. Non-epileptic seizures, e.g., psychogenic (not uncommon, Munchhausen syndrome, may mimic A-D), myoclonic (postanoxic, intoxication)

Guideline: Until proven otherwise, assume symptomatic etiology of A, B, C in a patient with no history of epilepsy. Perform a neurological examination including MRI, CSF examination, and clinical chemistry including blood glucose, vitamin B6 and substance abuse testing. In case of C, test for substance abuse and alcohol, particularly in the elderly. In a patient with a history of epilepsy, consider poor antiepileptic drug compliance, fever, or unrecognized progressive brain lesion, and a history of status epilepticus.

## Treatment Strategy:

1. Make sure you or a reliable witness have seen one indisputable epileptic seizure before you start treatment. If you are in doubt that the seizure has been epileptic, do not start or continue medication. Consider observing another seizure.
2. Write down the type of status (A-E) before starting treatment.
3. Write down the medication you give and what the patient has received earlier.
4. If you decide to initiate medical treatment, do it at full dosage, follow your house rules for treating status epilepticus.
5. Once status epilepticus has been interrupted, start the search for etiology
6. In case of non-convulsive absence status, monitor treatment effect by EEG 24 hours later because of the high relapse rate.

## Guideline

## Emergency on-site treatment:

A, B, D: Status epilepticus can be terminated by giving diazepam 10 to 20 mg (for adults) IV or up to 2 doses (if necessary) of lorazepam 4 mg IV. For children, IV diazepam up to 0.3 mg/kg or lorazepam up to 0.1 mg/kg is given. For adults, phenytoin 1.5 g IV may be given to prevent recurrence. Fosphenytoin, a water-soluble product, is an alternative that in equivalent doses reduces the incidence of hypotension and phlebitis

Select one Benzodiazepine (Diazepam i.v., rectal tube, Lorazepam i.v., Expidet, Clonazepam i.v.) followed by i.v. Phenytoin, transfer to immediate in-patient care.

C: Select one Benzodiazepine (Diazepam i.v., rectal tube, Lorazepam i.v., Expidet, Clonazepam i.v.) followed by i.v. Valproate, transfer to immediate in-patient care

E: No emergency antiepileptic drug treatment, recommend elective neurological and psychiatric evaluation

## In-patient treatment:

A, B, C, D: Anesthetic IV doses of phenobarbital, lorazepam, or pentobarbital may be necessary in refractory cases; in such instances, intubation and O<sub>2</sub> therapy are required to prevent hypoxemia. See algorithm

D: No aggressive parenteral treatment

E: No emergency antiepileptic drug treatment, recommend elective neurological and psychiatric evaluation

Prognosis: Expect seizure control in 80%, mortality may be as high as 30%, depends mainly on etiology.

Main errors: Wrong diagnosis, hesitant administration of too small doses of a number of agents, overlooking of medical complications e.g. acidosis.

sion. In every patient with uncontrolled epilepsy, a dose increment should be considered unless the patient has symptoms and signs of incipient central nervous system or other organ drug toxicity. It has been shown that in as many as one in three patients presenting with uncontrolled seizures, increasing the dose led to seizure remission [39].

*Recommendation. Treatment should be kept simple. Unnecessary diagnostic or therapeutic interventions with an unfavorable risk–benefit balance should be avoided. It is advisable to withhold drug treatment until the diagnosis of epilepsy is certain. Combination therapy and enzyme-inducing agents should be avoided, if possible. Both overtreatment and undertreatment should be avoided.*

### 3.13. Needs of special patient groups

One of the standards of good clinical care is to individualize the treatment of epilepsy according to the special needs of the individual with epilepsy which are outlined below. For further discussion, see [1–3,7].

#### 3.13.1. The elderly

The change in pharmacokinetics and the higher sensitivity to adverse events of many AEDs in the elderly usually require more cautious dosing in this segment of the population. In addition, high comorbidity in the elderly often requires additional medication. To avoid disturbing drug interactions, AED monotherapy and use of modern AEDs such as gabapentin, lamotrigine [40], and levetiracetam are preferable. It has been estimated that 10–12% of all nursing home residents receive AEDs; as a rule, the elderly with epilepsy are taken care of by family doctors. Compliance may be more difficult in the elderly with cognitive decline. Multimorbidity with lots of comedications is common. The elderly may have an increased susceptibility for adverse events, especially when treated with carbamazepine. Ataxia may be more frequent in the elderly, and discontinuation of AEDs because of adverse events is more common in the elderly than in younger adults. Lower doses of AEDs are often sufficient because treatment response may be better in the elderly. Lower glomerular filtration rates in the elderly require much lower doses of renally excreted AEDs. Body fat, albumin, and cytochrome P450 changes also occur in the elderly, and oxcarbazepine-related hyponatremia may be more frequent. Osteoporosis may be overlooked in the elderly with epilepsy who are on enzyme-inducing AEDs or valproate.

*Recommendation. Epilepsy in the elderly is increasing although specialists see surprisingly few elderly patients with epilepsy. If possible, treatment with nonmetabolized, non-enzyme-inducing new AEDs such as gabapentin, lamotrigine, and levetiracetam, instead of classic enzyme-inducing AEDs such as carbamazepine, is preferable. Slow dose escalation and lower-than-average dosages are recommended; AED combination therapy should be avoided, and clear written*

*instructions are important. Nonconvulsive status epilepticus may occur.*

#### 3.13.2. Adolescents

AED therapy in adolescence is often difficult because of the frequency of noncompliance in this segment of the population [1–3]. Many studies show that the factors that ensure good compliance are good motivation, a good therapeutic result, the support of parents, medical, and assistance personnel, and a positive attitude toward the disease and its treatment. Moreover, in recent years, many studies have reported the changes in endocrinology function and weight changes that occur in adolescents after AED therapy and, in particular, after long-term therapy with valproate, carbamazepine, gabapentin, and topiramate. Abnormalities include weight increase (valproate, gabapentin, pregabalin), weight loss (topiramate), possibly polycystic ovaries (valproate), and bone disease (osteopenia/osteoporosis and osteomalacia with carbamazepine, phenytoin, phenobarbital, and valproate). Weight remained stable in adolescents treated with lamotrigine or oxcarbazepine. Enzyme-inducing AEDs (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, topiramate >200 mg/day) may lower the efficacy of oral contraceptives, whereas gabapentin, levetiracetam, and valproate do not interact with oral contraceptives. Lamotrigine may impair the efficacy of oral contraceptives, and oral contraceptives may, lower the efficacy of lamotrigine through pharmacokinetic drug interactions. Folate supplementation (5 mg/day) is recommended in female adolescents prescribed valproate or carbamazepine. Adolescents often experience stress from the seizures, limitation of leisure activities, side effects of medication, and feelings of being different. The coping strategies include support and being in control. Paroxysmal nonepileptic events are frequently encountered in children and adolescents. Resective surgery for drug-resistant mesial temporal lobe epilepsy is as effective in adolescents as in adults.

*Recommendation. Juvenile myoclonic epilepsy begins during adolescence and is easy to control provided seizure-provoking agents such as lack of sleep, alcohol, and poor drug compliance can be avoided. JME requires lifelong therapy because of the very high recurrence rates (>90%) on discontinuation of AEDs in seizure-free patients. Easy-to-treat idiopathic partial epilepsy, as well as difficult-to-treat symptomatic epilepsy, for example, mesial temporal lobe epilepsy, which often requires surgery for complete control, is first observed during this stage of life. Management of adolescents with epilepsy is unique because adolescents often suffer stress not only from the seizures, but from the limitation of leisure activities, side effects of medication, reproductive issues, substance abuse, and feelings of being different.*

#### 3.13.3. Women

Epilepsy is equally prevalent in men and women; however, in women, epilepsy raises special reproductive and general health concerns [41]. Surveys show that women



are not receiving important information about their condition and the possible adverse effects of treatment, which could have profound implications for their health and the health of their unborn child. Women with epilepsy need regular review and should receive appropriate information about the impact of their treatment in a timely manner. Epilepsy is a common neurological disorder affecting women during the reproductive years. Although there exists a relationship between hormones and seizure activity in many women, good treatment options for catamenial epilepsy remain elusive. Women with epilepsy are at increased risk for reproductive disorders. Seizures and some AEDs can compromise reproductive health, and some AEDs can adversely affect carbohydrate and bone metabolism. Women with epilepsy have lower birth rates and more frequent anovulatory menstrual cycles. This appears to be related to seizure- and AED-associated reproductive endocrine disturbances. Carbamazepine, phenytoin, and phenobarbital induce hepatic cytochrome P450 enzymes and lower endogenous estrogens, adrenal and ovarian androgens, and contraceptive steroids. Valproate inhibits steroid hormone metabolism, elevates androgens, and predisposes to phenotypic signs of hyperandrogenism: hirsutism, obesity, acne, and frequent anovulatory cycles. It has been suggested that polycystic ovary syndrome is common in women treated with valproate. However, there is currently no Class I evidence that valproate contributes to the development of polycystic ovary syndrome. Valproate is, however, associated with weight gain, possibly through the alteration of insulin metabolism. No compelling data lead to a specific contraindication to the use of valproate in young women, and, after informed consent, drug remains a first-line treatment option, given its unsurpassed efficacy in idiopathic generalized epilepsies [27].

*Recommendation. Irregular menstrual cycles, anovulatory cycles, hirsutism, acne, and obesity should prompt an evaluation for reproductive dysfunction. After the start of valproate therapy in a woman with epilepsy, the length of the menstrual cycles and body weight should be monitored. Transvaginal ultrasonography of the ovaries is indicated if the menstrual cycles are prolonged and serum testosterone levels are elevated, especially if there is associated weight gain. The endocrine effects of the new AEDs have not been widely studied. However, treatment with these agents, such as lamotrigine, should be considered in women who develop reproductive endocrine dysfunction during treatment with the older AEDs.*

**3.13.3.1. Pregnancy.** Prepregnancy counseling should include information that enzyme-inducing AEDs lower the efficacy of oral contraceptives and lead to unplanned pregnancies [1–3, 41]. Alternative contraceptive measures should be taken in addition. A number of AEDs do not interact with oral contraceptives such as gabapentin and valproate. Women with epilepsy exposed to valproate have approximately twice the risk of the general population of bearing children with congenital malformations, whereas

women taking lamotrigine and carbamazepine have rates similar to those of untreated women with epilepsy or the general population. Valproate and carbamazepine have been associated specifically with the development of neural tube defects (NTDs), especially spina bifida. Other factors may contribute to the risk, including concomitant diseases such as diabetes mellitus, occupational exposure to teratogens, excessive prepregnancy weight, and various nutrient deficiencies. In the general population, maternal folate deficiency, in particular, has been linked to the development of neural tube defects, and periconceptional folate supplementation has been associated with a reduction of this risk. It is unclear whether folate supplementation has a comparable protective effect for women with epilepsy. Except for lamotrigine, data concerning the risk for congenital malformations associated with the newer AEDs (gabapentin, felbamate, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) are still limited. Despite uncertainty about the efficacy of periconceptional folate supplementation in women with epilepsy, supplementation at dosage levels of, for example, 5 mg/day, is recommended for the general population of women of childbearing age. Seizure control must not be neglected in pregnant women with epilepsy, as seizures are associated with harm to the fetus as well as the mother. Risk may be minimized by using a single AED at the lowest effective dosage. Although the role of AED therapy in teratogenesis has been widely investigated, there are few prospective studies on later postnatal development in offspring of epileptic women exposed in utero. The role of high-resolution ultrasound examinations in the prenatal detection of fetal abnormalities should be discussed. Monotherapy with the lowest effective dosage of an AED should be implemented, if possible. Also, the diagnosis of epilepsy and the need for AED treatment should be reevaluated. Women should be reassured that with a multidisciplinary approach, more than 90% of all offspring are normal.

If a woman presents for the first time in pregnancy weeks 10–14, as is often the case, the prepregnancy AED treatment should be continued, because organ formation has been completed. The woman should be reassured about the general good outcome, and specific measures such as serum  $\alpha$ -fetoprotein measurement, ultrasound examination, and possibly amniocentesis should be discussed. The patient should be cared for by a team of obstetricians, gynecologists, and neurologists in an effort to ensure the best treatment. With good drug compliance, no increase in seizure frequency is seen during pregnancy. AED dosage adjustments may be necessary during pregnancy and should be based on clinical symptoms, not entirely on serum drug concentrations. Women taking enzyme-inducing anticonvulsants should take oral vitamin K (10 mg/day) in the 4 weeks before the expected date of delivery to reduce the risk of hemorrhagic complications in the child. The vast majority (>90%) of pregnant women with epilepsy give birth without complications, and cesarean section is rarely necessary. To avoid seizures during labor,

some physicians add 10 mg clobazam to the AED regimen when labor starts. During the puerperium, the dose of AEDs may need to be lowered because plasma AED concentrations may increase and cause central nervous system toxicity. Children should be breastfed to reduce the risk of sudden anticonvulsant withdrawal and to provide the general benefits of breastfeeding.

*Recommendation.* Enzyme-inducing AEDs may lower the efficacy of oral contraceptives. Women with epilepsy may suffer from gender-specific reproductive dysfunction to which enzyme-inducing AEDs and valproate may contribute, at least partly. Although the outcome of pregnancy is normal in 90%, folate substitution and use of the lowest effective dose of the AED are advisable. Although exposure to valproate during early pregnancy is associated with an increased risk of malformations, 90% of the children born have no such malformations, and the risk–benefit balance needs to consider the unsurpassed efficacy of valproate for idiopathic generalized epilepsies. The fetal AED syndrome(s) need also to be mentioned when discussing AED-associated risks. Breastfeeding is advisable.

**3.13.3.2. Menopause.** Menopausal women with epilepsy pose several unique management challenges [1–3, 41]. They have an elevated risk for osteoporotic fractures because of the adverse effects of AEDs on bone metabolism, combined with the chance of trauma during seizures and the subtle effects of AEDs on coordination that promote falling. Most, but not all, prior cross-sectional studies have reported that patients taking AEDs have lower bone mass density than healthy control subjects. With the exception of age, gender, and weight, prior cross-sectional studies have also been limited by their ability to control for factors such as health status, physical activity, calcium and vitamin D intake, estrogen use, and physical function that may confound or modify the association between AED use and bone mass density. Finally, prospective studies are needed to accurately determine the association between AED use and rates of bone loss because potential biases in cross-sectional data. Carbamazepine, phenobarbital, phenytoin, and valproate, but not lamotrigine, are associated with lower levels of calcium. Phenytoin, but not valproate or lamotrigine, appears to accelerate bone turnover. AED effects on bone mineral metabolism may explain the elevated risk of fractures described in women with epilepsy. A uniform effect of AEDs on vitamin D metabolism or bone turnover has not yet been revealed by clinical or experimental studies, although the enzyme-inducing AEDs appear to decrease serum vitamin D levels. However, bone density is frequently decreased in patients with epilepsy. Clinicians should be familiar with the recommendations for calcium and vitamin D supplementation and recognize when to refer patients for bone density evaluations. Perimenopause is the transition during which some women with epilepsy are at risk for increased seizure frequency, probably because of alterations in the estrogen/progesterone ratio during this period. Hormone replacement therapy

may also increase seizure occurrence. Finally, women with poorly controlled seizures may enter menopause at an earlier age.

*Recommendation.* Arthralgias and muscle pain may indicate osteoporosis in menopausal women with epilepsy. During menopause, osteoporosis may require treatment.

#### 3.13.4. Men

Men with partial epilepsy, especially temporal lobe epilepsy, have been found to have an increased risk of erectile dysfunction [1–3, 41]. These findings have been attributed to epilepsy itself, but antiepileptic drugs also have various effects on male endocrine function. Among 40- to 50-year-old men with partial epilepsy taking enzyme-inducing AEDs, 9 of 10 have low bioactive testosterone levels as compared with 1 of 3 taking lamotrigine and 1 of 3 healthy controls taking no AED. Sexual function, as measured by bioactive testosterone levels, is greater with lamotrigine than with enzyme-inducing AEDs. Abnormally low bioactive testosterone levels are reached at an earlier age with enzyme-inducing AEDs than with lamotrigine. Carbamazepine appears to decrease the bioactivity of androgens, whereas oxcarbazepine below 900 mg/day does not. Men with epilepsy have reduced fertility, and antiepileptic drugs may affect semen quality. Carbamazepine, oxcarbazepine, and valproate are associated with sperm abnormalities in men with epilepsy. In addition, valproate-treated men with generalized epilepsy who have abnormal sperm may have reduced testicular volume. Finally, epilepsy itself may negatively affect male endocrine function, and successful temporal lobe epilepsy surgery may lead to a normalization of serum androgen concentrations in men with epilepsy. Long-term AED therapy in young male patients who have seizures causes significant bone loss at the hip in the absence of vitamin D deficiency. Obese valproate-treated men have high serum insulin levels, indicating insulin resistance. Moreover, some of the valproate-treated men cluster cardiovascular risk factors such as obesity, hyperinsulinemia, and elevated serum triglyceride concentrations. Carbamazepine and oxcarbazepine do not seem to have any significant effects on serum insulin or lipid levels in men with epilepsy.

*Recommendation.* Men with epilepsy often experience sexual dysfunction and weight gain. Enzyme-inducing AEDs may lower bioactive testosterone levels and, together with AED-associated sedation, contribute to sexual dysfunction. It is therefore advisable to avoid sedative and enzyme-inducing AEDs in men with epilepsy; weight-neutral and non-enzyme-inducing AEDs are preferable.

#### 3.13.5. Persons with mental health disorders

The lifetime community-based prevalence of depression, suicidal ideation, and generalized anxiety disorder is two-fold higher in patients with epilepsy compared with the general population (see Section 2.9). Suicide is a leading cause of death in patients with refractory epilepsy. Depression and—less well known—anxiety disorders are the lead-

ing causes of suicidal death in epilepsy. Severity of depression (not seizure frequency) seems to be the most important correlate for quality of life. Serotonin reuptake inhibitors can be given for depression in persons treated with AEDs for epilepsy without worsening seizure control. Treatment of depression does not seem to affect seizure control either way. Reboxetine and citalopram are good candidate antidepressants for people with epilepsy. Anxiety can be treated with anxiolytic agents such as buspirone (10–20 mg / day). In patients with uncontrolled epilepsy and anxiety who require a change in AED regimen, add-on treatment with anxiolytic AEDs such as pregabalin may be considered. In patients with dysthymia and mood instability, mood-stabilizing AEDs such as lamotrigine and valproate should be considered, particularly when a change in regimen is required to improve seizure control. Conversely, treatment with phenytoin or phenobarbital has been shown to be associated with depression and mood disorders in some patients, even when treatment has resulted in seizure freedom. If both seizure control and mood stability prove resistant to treatment with AEDs, vagus nerve stimulation should be considered. Vagus nerve stimulation has been shown to improve seizure control and mood, particularly postictal mood changes. In patients undergoing resective surgery for refractory epilepsy, particularly refractory temporal lobe epilepsy, those who become seizure free after surgery often report improved mental well-being. It is difficult to say at present if the improvement in mood is a specific effect of surgery or if it also is due to the seizure freedom brought about by the change in AED regimen in apparently refractory partial epilepsy.

*Recommendation. Depression and particularly anxiety are often underdiagnosed in patients with epilepsy, especially drug-resistant epilepsy. Treatment with serotonin reuptake inhibitors and anxiolytic agents such as buspirone is as safe and effective as in a patient without epilepsy. It is advisable to avoid classic AEDs such as phenytoin and phenobarbital, which may contribute to depressive mood, and to prefer new, mood-stabilizing AEDs such as lamotrigine or anxiolytic AEDs such as pregabalin. Vagus nerve stimulation should be considered if seizures and depression prove to be resistant to drug treatment.*

### 3.14. Stopping treatment

About 4–6 of 10 patients without seizures can eventually discontinue AEDs without relapse, but even with continued drug treatment, relapse occurs in about 3 of 10 patients [42]. With the observed relapse rate (on and off drugs), long-term complete seizure control off AEDs can be expected in no more than 1 of 3 patients with new-onset epilepsy. Although reinstatement of AEDs after a recurrence following planned discontinuation in seizure-free patients is successful in about 80% of patients, it is associated with the risk that seizure control will not be regained in about 20%. Also, response to AEDs may occur as late as 12 years after restarting treatment in some patients. These risks

must be mentioned when discussing AED discontinuation or taper with seizure-free patients. Higher-than-average relapse rates are seen in patients who take a long time to become seizure free; those with symptomatic partial or generalized epilepsy and juvenile myoclonic epilepsy and those with important social reasons for avoiding seizures should be treated indefinitely.

*Recommendation. Except for benign idiopathic epilepsy of childhood, planned discontinuation of AEDs in seizure-free patients should not be encouraged. The risk of recurrence is high (up to 3/10 for children and 6/10 for adults). In addition, return to AED treatment guarantees neither complete nor rapid seizure control in as many as 2 of 10 patients with a seizure recurrence.*

## 4. Nonpharmacological therapy

Nonpharmacological therapy of the epilepsies is usually adjunctive, either by preventing seizure precipitation or through surgery. Resective surgery of localized seizure-generating tissue is a standard procedure for drug-resistant partial epilepsy, mostly for mesial temporal lobe epilepsy [43]. Palliative procedures include vagus nerve stimulation; a number of other nonpharmacological procedures such as brain stimulation and radiotherapy are still experimental.

### 4.1. Avoiding seizure precipitation

Nonpharmacological measures play an important supporting role in seizure regulation in individually susceptible patients, mostly adolescents with juvenile idiopathic generalized epilepsies. Disturbances in their sleep–wake cycle, especially reduction of sleep, may provoke seizures the next morning. Following a regular sleep schedule is helpful; pragmatically, sleep onset should not vary by more than 2 hours. Sleep reduction, often combined with partying and substance abuse or stress, is a common precipitating factor in adolescents and adults with a first epileptic (mostly GTC) seizure. In some of these patients, regular sleep and a less stressful lifestyle may be enough to prevent further seizures. In addition, AEDs may not be able to achieve seizure control if the lifestyle is not changed. In altogether rare reflex epilepsies, specific precipitants of seizures may be the targets of nonpharmacological intervention. For example, most patients with primary reading epilepsy begin to have, with prolonged reading, perioral reflex myoclonias, which enable them to stop reading and, thus, to avoid a GTC seizure. In photosensitive patients, seizures are often precipitated by television. These can be avoided by viewing from a distance and using a remote control and by using small screens in a well-lit room, and preferably with a 100-Hz line shift. Environmental flicker stimulation often comes unexpectedly, and it is advisable that patients always wear sunglasses in brightly lighted surroundings. Polarized glasses seem to be more protective than plain sunglasses. If the patient has only photically induced seizures, specific prevention

alone may be sufficient treatment, but when spontaneous seizures also occur, drugs are usually needed in addition. Some patients with partial seizures with an extended aura claim that they know how to prevent seizure spread with various nonspecific measures such as relaxation, concentration, or a combination of both. It is often difficult, however, to support such claims.

#### 4.2. Resective surgery

Adjunctive resective surgery is a standard of care for properly selected patients with drug-resistant partial epilepsy, especially mesial temporal lobe epilepsy [43]. About 10 to 20% of patients have severe disabling seizures that are refractory to medical treatment. Most of properly chosen patients whose seizures originate from a local area of abnormal brain function improve markedly when the epileptogenic tissue is resected. The surgical approach chosen depends on many considerations including mainly the localization and the extent of the epileptogenic zone, MRI findings, and the risk–benefit balance of the resective surgery itself, and preoperative monitoring (Fig. 11) [43].

Approximately 25–30% of patients with temporal lobe epilepsy are cured in the long run and no longer require AEDs for seizure freedom; another 25–30% become seizure free or nearly seizure free with continued drug treatment [44,45]. Because extensive monitoring and skilled medical–surgical teamwork are required, these patients are best managed in specialized centers. Mesial temporal lobe epilepsy is the most common surgically remediable refractory partial epilepsy. Medical treatment cannot achieve seizure freedom in an estimated 75% of cases, and with surgical treatment and AEDs, 50% become seizure free, as noted earlier. Mesial temporal lobe epilepsy has been well characterized and can usually be identified with noninvasive studies including scalp electroencephalography and video monitoring with ictal recording, MRI, SPECT, positron emission tomography, neuropsychological assessment, and historical and clinical data. Sometimes, an invasive EEG is needed to confirm mesial temporal lobe seizure onset, which, combined with the underlying pathological abnormality (the substrate) of mesial temporal sclerosis (hippocampal neuronal loss and gliosis), defines mesial temporal lobe epilepsy.

Compelling short-term evidence exists including the only randomized controlled trial comparing surgery plus AEDs with AEDs alone [43,46]. The patients were randomized prior to presurgical evaluation, so the study allowed intent-to-treat analysis. At 12 months after surgery, 15 of 40 surgical patients (including 4 patients who were randomized to surgery but were not operated on) and 1 of 40 medical patients were free of seizures as defined by the authors [46]. The number of patients needed to treat for one patient to become free of disabling seizures while remaining on AEDs is 2, which is superior to most interventions in neurology. A meta-analysis of nonrandomized trials provided almost identical results; about two-thirds










Epilepsy Surgery	
Procedure	Clinical Use
Selective Amygdala-hippocampectomy 	Ammonshornsclerose or other pathology of the mesial temporal lobe
Tailored Temporal lobe resection 	Temporal lobe lesions or cryptogenic temporal lobe epilepsy
Topectomy (Lesionectomy) 	Extra-temporal lobe lesions
Hemispherectomy Hemispherotomy 	Hemispheric lesions or encephalitis
Topectomy transections* 	Lesions close to eloquent brain areas
Subpial transections* 	Lesions in eloquent brain areas
Isolated lobar resection* 	Extended lesions (developmental, post-encephalitic)
Multiple lobar Resections* 	Extended lesions (developmental, post-encephalitic)
Callosotomy* (Two-thirds or total) 	Drop attacks (Lennox-Gastaut-Syndrome)

Fig. 11. Overview of procedures for epilepsy surgery. \* indicates mostly palliative interventions which rarely result in complete seizure freedom, this includes callosotomy which is thought to stop drop attacks (for discussion [see 3,41]).

of patients become seizure free with continuing AED treatment, compared with only 8–24% with medical therapy. The results are remarkably similar among studies from different parts of the world. Several supportive studies employing nonrandomized medical controls showed that surgical treatment of drug-refractory temporal lobe epilepsy in properly selected patients is superior to continued medical treatment [47,48]. The mechanism(s) by which the resection is able to transform drug-resistant epilepsy into drug-responsive epilepsy (with seizure freedom on or off AEDs) is unclear.

Quality of life improves early after epilepsy surgery; the improvements are both statistically and clinically significant. Surgical morbidity with clinically important perma-

ment sequelae is 2%. In addition, successful temporal lobe epilepsy surgery appears likely to reduce the risk of seizure-related death. However, it remains largely underused and overly delayed, partly because of the legitimate fears of possible surgical complications, such as verbal memory deficits and failure to control seizures. Reasons for surgical failures are not completely understood, and include bitemporal, pseudotemporal, and so called temporal plus epilepsies, as well as insufficient resection of the mesial temporal structures. Although there are similar Class IV results for localized neocortical resections, no Class I or II studies are available. Further studies are needed to determine if patients with neocortical seizures benefit from surgery, to determine whether early surgical intervention should be the treatment of choice for certain surgically remediable epileptic syndromes, and to better define precise predictors of surgical success [43].

Seizure recurrence has been noted during a 5-year follow-up in approximately one-third of these seizure-free patients after temporal lobe resection, mostly but not exclusively following planned complete discontinuation of AEDs [49]. This leaves one-third of patients without disabling seizures and without AEDs several years after surgery. Despite improvements in seizure frequency or severity, seizures persist in another third of patients undergoing surgery. We need a long-term randomized controlled trial on AED discontinuation in seizure-free patients followed by long-term open extension to determine if only one in three adult patients with drug-resistant temporal lobe epilepsy is cured by surgical intervention [45].

*Recommendation. Resective epilepsy surgery is the only chance for 6 of 10 patients with suitable drug-resistant temporal lobe epilepsy to become seizure free with continued AED use, whereas fewer than 1 of 10 become seizure free with continuation of AEDs alone. In one-third of patients, AEDs can be safely withdrawn. Surgical outcome in partial epilepsy originating from other lobes may be less successful but still worthwhile.*

#### 4.3. Neurostimulation

##### 4.3.1. Brain stimulation

Brain stimulation has been investigated for more than 50 years as a treatment option for patients with medically refractory seizures who cannot be offered epilepsy surgery due to multiple foci or overlap between the epileptogenic zone and eloquent cortical areas. It is still in an experimental stage. In recent years, stimulation of the subthalamic nucleus, the centromedian nucleus of the thalamus, the anterior thalamus, the hippocampus, and the cortex has received most interest. Stimulation was performed in a small number of patients, and seizure reduction was noted in some patients [50].

##### 4.3.2. Vagus nerve stimulation

Vagus nerve stimulation, intermittent electrical stimulation of the left vagus nerve with an implanted pacemaker-

like device, reduces the number of partial seizures by one-third with continued AED therapy. After the device is programmed, patients can activate it with a magnet when they sense a seizure is imminent. Vagus nerve stimulation is used as an adjunct to AED treatment when resective surgery is not feasible or has been unsuccessful. Adverse effects include a deepening of the voice during stimulation, cough, and hoarseness, which disappear within several months in most patients. Complications are minimal. Use in other than partial epilepsy is not well established.

*Recommendation. Vagus nerve stimulation is a reasonable palliative alternative if surgery is not possible or has failed. The onset of action is delayed for several months; complications are minimal.*

#### 4.4. Ketogenic diet

The ketogenic diet is a very low carbohydrate, adequate-protein, high-fat diet used to treat refractory epilepsy since the 1920s. It requires a devoted multidisciplinary approach, which includes physicians, nurses, social workers, dieticians, and parents. The diet mimics the biochemical changes associated with starvation, which create ketosis. Although less commonly used in later decades because of the increased availability of anticonvulsants, the ketogenic diet has reemerged as a therapeutic option if AEDs fail to control seizures and surgery is not an option. The ketogenic diet should be continued for 1 or 2 years, if effective. It should be considered as alternative therapy for children with refractory epilepsy. Only a decade ago, the ketogenic diet was considered a last resort. Although no randomized controlled trials have been performed, large observational studies, some prospective, suggest an effect on seizures. These effects require validation in randomized controlled trials. It has become more commonly used in academic centers throughout the world. The Atkins diet is a recently used, less restrictive therapy that also creates ketosis and may be able to reduce the number of seizures. Dietary therapies may become even more valuable in the therapy of epilepsy when the mechanisms underlying their success are better understood. Although the ketogenic diet has been shown to be useful in the treatment of childhood epilepsy, the long-term effects of the ketogenic diet on nutritional status and brain development are not clear. Bicarbonate levels should be monitored carefully in patients treated with both topiramate and the ketogenic diet, and bicarbonate supplements given when symptomatic. Excessive bruising is a symptom noted by parents of some children treated with the ketogenic diet. Patients on the diet undergoing anticoagulation or surgery should be evaluated carefully for symptoms of bleeding tendency. The ketogenic diet may be associated with nephrolithiasis in some patients. The effect of the ketogenic diet on seizures requires validation in randomized controlled trials. For those with a difficult-to-treat epilepsy on multiple

antiepileptic drugs, the ketogenic diet is a possible option [51].

*Recommendation.* The ketogenic diet is an option for drug-resistant epilepsy, particularly in children, when better proven treatments such as resective surgery and vagus nerve stimulation are not possible.

#### 4.5. Complementary medicine

The large percentage of patients whose seizures are refractory to AEDs and who undergo resective surgery or medical device implantation may perhaps explain why patients with epilepsy turn to complementary medicine as a last resort. Complementary and alternative medical therapies include chiropractic, acupuncture, yoga, diet, homeopathy, acupuncture, biofeedback, traditional Oriental medicine, aromatherapy (with or without hypnosis), massage therapy, herbal remedies, mind–body therapies (such as meditative practices and visualization, Reiki-like healing practices), and folk practices and religious healing. Of these, modalities based on spiritual healing create a number of conundrums for the clinician, including legal, regulatory, and ethical issues. Magnets, electric currents, and artificial electromagnetic fields have also been used to treat patients with epilepsy. Psychological interventions such as relaxation therapy, cognitive-behavioral therapy, electroencephalography, biofeedback, and educational interventions have been used alone or in combination in the treatment of epilepsy, to reduce seizure frequency and improve quality of life. Anecdotal accounts suggest that some herbal substances may have anticonvulsant effect, but randomized double-blind controlled trials are lacking. Alternatively, many herbals and dietary supplements may predispose to seizures in individuals without epilepsy and worsen seizure control in those with epilepsy. It remains to be seen whether perceived positive outcomes of complementary medicine could be explained by enhancement of the placebo effect or specific action, if any. In view of methodological deficiencies and limited number of individuals studied, there seems to be no reliable evidence to support the use of any of these treatments; randomized controlled trials are needed.

*Recommendation.* Complementary medicine is often sought when and if AEDs have failed to control seizures despite toxicity from high doses, and surgery is not possible or declined. AED treatment should be continued when complementary medicine is used. The toxicity of unproven complementary medicine is often underestimated.

#### 4.6. Future treatment scenarios

Current AEDs suppress seizures without influencing the underlying tendency to generate seizures. One major aim in understanding how epilepsy develops is to prevent it [52]. Clinically, there is often a “silent interval” between the occurrence of a neurological insult and recurrent seizures in many acquired forms of epilepsy. In addition, most

genetically determined epilepsy syndromes do not become clinically manifest until well after birth. Both these facts suggest that epileptogenesis is a gradual process that can be specifically targeted. Ideally, we would like to have a drug that prevents the development of epilepsy, rather than one that merely suppresses seizures. Unfortunately, none of the available anticonvulsant agents appear to have a prophylactic effect in patients who are at risk for the development of a seizure disorder.

Drug treatment of epilepsy is characterized by unpredictability of efficacy, adverse drug reactions, and optimal doses in individual patients, which, at least in part, are a consequence of genetic variation. Since genetic variability in drug metabolism was reported to affect treatment with phenytoin more than 25 years ago, numerous studies have explored how variation in genes alters the pharmacokinetics and, more recently, pharmacodynamics of AEDs, suggesting that a wide assortment of genetic variants influence how individuals respond to AEDs. Advances in the management of epilepsy include pharmacogenetic studies that predict the Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with carbamazepine treatment in Asians and patients of Asian ancestry with the HLA-B\*1502 allele [53]. Genetic tests for HLA-B\*1502 are already used to check for compatibility before tissue transplants. This finding has important implications for clinical practice. Patients with ancestors from areas in which HLA-B\*1502 is present should be screened for the HLA-B\*1502 allele before starting treatment with carbamazepine. According to an alert from the Food and Drug Administration [53], carbamazepine should not be started if the patient tests positive unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing because of carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B\*1502 [53]. Patients who test positive for HLA-B\*1502 may be at increased risk of SJS/TEN from other AEDs that have been associated with SJS/TEN. Therefore, for HLA-B\*1502-positive patients, doctors should consider avoiding the use of other AEDs associated with SJS/TEN when alternative therapies are equally acceptable [53]. Tested patients who are found to be negative for HLA-B\*1502 have a low risk of SJS/TEN with carbamazepine, but SJS/TEN can still rarely occur, so health care professionals should still watch for symptoms in these patients. More than 90% of carbamazepine-treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. Patients of any ethnicity or genotype (including HLA-B\*1502-positive patients) who have been taking carbamazepine for more than a few months are at low risk of SJS/TEN from carbamazepine. Pharmacogenetic studies hold the promise of being able to better individualize treatment for each patient, with the maximum benefit and the minimum risk of adverse effects.

## 5. Conclusions

The epilepsies are among the most common serious chronic disorders of the brain. Presentations differ widely due to different seizure types, syndromes, causes, comorbid conditions, and other individual patient factors. Fortunately, up to 70% of patients will have their seizures controlled with drugs, which makes epilepsy one of the best treatable chronic conditions of the brain. However, the remainder continue to have seizures and their negative effects on quality of life, morbidity, and risk of mortality. Surgical treatment is life changing for a small proportion of properly selected patients. A better understanding of what causes epilepsy will move treatment from seizure suppression to prevention of epilepsy. Pharmacogenetic studies hold the promise of making it possible to better individualize treatment for each patient, with maximum benefit and minimum risk of adverse effects. We believe that what happens every day in the care of individuals with epilepsy deserves the most attention. People with epilepsy need empathy and sympathetic, holistic care that integrates science with the personal needs of the individual.

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