Epilepsy: Mechanisms of Drug Action and Clinical Treatment

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EPILEPSY: MECHANISMS OF DRUG ACTION AND CLINICAL TREATMENT

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14.1 INTRODUCTION

The epilepsies are a group of chronic neurological conditions characterized by the episodic occurrence of one or more kinds of seizures, which result from the abnormal, synchronous firing of large ensembles of neurons in the brain. Epilepsy is one of the most common neurological disorders, affecting approximately 0.6% of the population in high-income countries [1]. The incidence and prevalence may be higher in lower income regions; the parasitic disease cysticercosis, for example, is a common cause of epilepsy [2]. Patients with uncontrolled epilepsy may suffer severe social, neuropsychological, and economic problems; epilepsy continues to be a stigmatizing disorder, even in industrialized countries [3]. Moreover, patients suffer from increased mortality, due to accidents, suicide, and “sudden unexplained death” [4].

Seizures can be provoked by drugs, such as cocaine, phencyclidine, isoniazid, theophylline, cyclosporin A, and lidocaine; the withdrawal of alcohol, benzodiazepines, or barbiturates; metabolic derangements such as uremia, hypoglycemia, nonketotic hyperglycemia, hyponatremia, and hypocalcemia; and acute head trauma. A person with seizures that occur only in the setting of such transient reversible disorders is not considered to have epilepsy.

The diagnosis of epilepsy is reserved for patients who have had two or more unprovoked seizures. Depending on risk factors such as the presence of a brain lesion or electroencephalographic abnormality, 16–62% of individuals experiencing their first unprovoked seizure will have a second unprovoked seizure within five years [4a]. For many epidemiological studies, patients with a previous diagnosis of epilepsy who have had at least one seizure in the past five years or are taking antiepileptic drugs (AEDs) are considered to have “active epilepsy” [1].

Most clinicians do not treat individuals who have experienced an isolated, unprovoked seizure when there is no evidence of neurological injury, structural abnormality on neuroimaging, abnormality in the electroencephalogram (EEG), or family history of epilepsy. However, individual considerations, including the potential physical, psychological, and vocational consequences of further seizures and of AED therapy, may influence clinical practice.

14.2 ANTIEPILEPTIC DRUGS AND CLINICAL EPILEPSY TYPES

AEDs are the mainstay of epilepsy therapy, although in selected cases surgery is an option. AEDs reduce seizure occurrence but are not known to influence the course of the underlying condition. The efficacy of AEDs is related to both clinical seizure type and epilepsy syndrome classification (based on clinical, electrophysiological, and imaging data). Clinical seizures are broadly classified into partial, beginning with electrical discharges in a limited area of the brain, and generalized, which begin with widespread electrical discharges that involve both sides of the brain at once. Partial seizures are further classified as to whether consciousness (the ability to respond and remember) is impaired (“complex”) or preserved (“simple”). Generalized seizure types include absence, atypical absence, myoclonic, atonic, tonic, clonic, and tonic–clonic. Partial seizures may undergo secondary generalization, in which the localized seizure discharge spreads and generalized tonic–clonic (or more rarely, tonic or
clonic) seizures occur. AEDs may be effective for one clinical seizure type but not another; phenytoin, for example, alleviates partial but not absence seizures.

Although there are a wide variety of syndromes, three broad groups can be discerned: primary generalized epilepsies, secondary generalized epilepsies, and localization-related epilepsies (Table 14.1). Some AEDs, such as ethosuximide in primary generalized absence epilepsy or adrenocorticotropic hormone (ACTH) in patients with infantile spasms, seem to have syndrome-specific effects.

Childhood-onset absence is the paradigmatic example of primary generalized epilepsy. Affected children may have multiple absence seizures during the course of the day. Absence seizures are characterized by brief (less than 10–20 s) loss of consciousness and, in some cases, eye blinking and slight movement of the mouth or extremities. Absence seizures are associated with 3-Hz spike-and-slow-wave complexes on the EEG and are believed to be caused by abnormal burst firing and oscillatory rhythms in thalamocortical circuits. In general, cognitive and neurological functions are normal, and most patients respond to AED therapy [5].

Patients with secondary generalized epilepsy syndromes, in contrast, may have severe neurological disorders such as tuberous sclerosis, ceroid lipofuscinosis, or Lafora disease. The prognosis is related to the underlying etiology. Even when no specific disorder is present, however, seizures are difficult to treat with AEDs, and additional therapies such as the ketogenic diet may be entertained. Since a clear epileptic focus can be identified only rarely, surgery is an option in a very limited number of cases.

Focal, or localization-related, epilepsies can be due to anything causing focal brain injury, such as trauma, tumors, or encephalitis. However, no underlying cause is apparent in the majority of cases. The most common form of localization-related epilepsy may be temporal lobe epilepsy (TLE). About 50% of patients have a lesion known as mesial temporal sclerosis, characterized by neuronal loss and gliosis in mesial temporal structures (MTSs). In addition to focal or “partial” seizures, patients with localization-related epilepsy may have secondary generalized seizures due to spread of epileptiform discharges. It is interesting that almost all AEDs used in these patients are more effective against the secondarily generalized seizures than the CPSs. Typically, patients with TLE may have several CPSs per week, but no GTCSs for years, as long as they take their AEDs. Focal resective surgery may be very effective for carefully selected patients with TLE [6, 7].

14.3 CLINICAL INVESTIGATION OF EPILEPSY

The patient’s seizure history, family history, and neurological examination can provide important data for epilepsy classification and prognosis. Neuropsychological testing is an important extension of the clinical examination. Deficits in modalities that show functional brain lateralization may help to identify focal epilepsies. Fluctuating test performance may suggest the effects of seizure clusters or AED toxicity, while secular decline can correlate with a worsening epileptic syndrome or underlying progressive etiology [8–10].

The EEG is the most important laboratory test to both detect the presence of a seizure disorder and identify seizure foci in patients with intractable epilepsy being considered for surgery. Early studies suggested that more than 90% of patients will
<table>
<thead>
<tr>
<th>Epilepsy Type</th>
<th>Etiology</th>
<th>Clinical Seizure Types</th>
<th>Other Clinical Features</th>
<th>Electroencephalogram</th>
<th>Structural Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary generalized epilepsy</td>
<td>Most unknown, presumed genetic; rare ion channel genes implicated</td>
<td>Absence; myoclonus; GTCS</td>
<td>Neurological and neuropsychological exam usually normal</td>
<td>Interictal normal; ictal shows regular generalized spike wave</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Secondary generalized epilepsy</td>
<td>Wide range of etiologies, including metabolic disorders, cortical malformations, phakomatoses; many unknown</td>
<td>“Atypical absence” myoclonic, tonic, clonic infantile spasms, GTCS, CPS</td>
<td>Highly variable features related to underlying disease; often developmental, neuropsychological, impairment</td>
<td>Intercital slowing and frequent widespread epileptiform discharges; ictal records often show irregular generalized spike wave discharges</td>
<td>May show wide range of structural and developmental abnormalities</td>
</tr>
<tr>
<td>Localization-related (focal)</td>
<td>Focal lesions resulting from developmental defects, trauma, infection, or neoplasms</td>
<td>SPS, CPS, GTCS</td>
<td>May have functional deficits related to seizure focus; usually mild</td>
<td>Focal interictal discharges; ictal discharges begin locally, may generalize</td>
<td>Focal abnormalities may include limited cortical dysplasia, tumors, “mesial temporal sclerosis”</td>
</tr>
</tbody>
</table>

*Abbreviations:* GTCS, generalized tonic-clonic seizure; CPS, complex partial seizure; SPS, simple partial seizure.
have an abnormal EEG if enough studies are performed [11]. In contrast, less than 3% of patients with no clinical history of seizures had “epileptiform discharges” on initial EEG; 14% of this group later developed epilepsy. Preoperative ictal video-EEG monitoring is used to detect localized seizure onset. In contrast to its diagnostic value, the EEG is used less often to assess the effect of AED therapy [12]. Patients whose clinical seizures are well-controlled can still have interictal EEG discharges, and it has not been shown that trying to suppress these, except in certain restricted instances such as childhood absence epilepsy, provides any therapeutic advantage [13].

AEDs with adverse cognitive effects, such as barbiturates and benzodiazepines, lead to increased β and δ activity on the EEG, but impairment is generally best detected by clinical examination [14].

The main advantage of magnetoencephalography (MEG) is that MEG signal propagation is much less affected by intervening tissue than for EEG so that sources that are not accessible to the EEG may be localized. Coregistration with magnetic resonance imaging (MRI) enhances identification of deep cortical generators of surface-recorded MEG signals. In some cases, MEG may provide better interictal and ictal spike localization and contribute to presurgical evaluation [15].

Neuroimaging has led to a revolution in the treatment of epilepsy and enhanced our understanding of the disease. MRI and positron emission tomography (PET) can detect underlying pathology and focal functional deficits in most patients with localization-related epilepsy. Computed tomography (CT) scanning is much less sensitive and only used to detect central nervous system (CNS) calcifications or other special situations. MRI should be performed in all cases, with the exception of primary generalized childhood absence. PET glucose metabolism and ictal single-photon emission computed tomography (SPECT) blood flow scanning are only performed for presurgical evaluation or research. PET receptor imaging has shown altered benzodiazepine or serotonin receptor binding in patients with focal epilepsies [16, 17]. So far, however, these data have not led to specific pharmacological interventions. MRI has shown evidence for progressive structural changes and FDG–PET progressive metabolic dysfunction in patients with uncontrolled epilepsy, reinforcing the case for aggressive early intervention to prevent neuronal injury from persistent seizures [18, 19].

14.3.1 Prognosis of Epilepsy

It is important to try to predict the prognosis of epilepsy both at the time of first presentation and after initial AED treatment has failed. Several difficulties arise, however. The natural history of untreated epilepsy is unknown, as at least some effective drugs have been available for more than 100 years. Experience in low-income countries, where the majority of patients receive no therapy, suggests that about 30% of patients may experience spontaneous remission or at least a fluctuating clinical course with long seizure-free intervals [20]. Several factors influence recurrence after a single seizure. Patients with symptomatic epilepsy, associated with a brain lesion or injury, have higher recurrence rates than those with no apparent cause or an avoidable precipitant such as transient metabolic derangement [4a]. Recurrence is much higher when a patient has had more than a single seizure: about 75% versus 40% at five years [4a]. Most studies suggest that 60–70% of patients with
“localization-related” epilepsy will become seizure free on AEDs, although the course may fluctuate [21, 22]. Clinical characteristics such as younger onset age may predict an increased risk that seizures become refractory to AED treatment [23]. Patient with primary generalized epilepsy may have a better, and secondary generalized epilepsy a worse, prognosis. Adverse social and psychological effects of epilepsy may persist even if patients eventually become seizure free, particularly when frequent seizures occurred during childhood and adolescence [24].

Randomized studies of early versus delayed treatment of patients who have suffered one or two seizures found a reduction in short-term seizure frequency but no difference in long-term prognosis [25, 26]. However, many neurologists treating patients with epilepsy believe that early intervention and seizure control may help to alleviate the social and neuropsychological consequences of epilepsy, although the risks of AED toxicity have to be considered. There has been increasing recognition that simply suppressing seizures with AEDs may not stop the progression of the underlying epileptic disorder. Conceivably, it may be possible to intervene after a precipitating event such as brain injury to stop the development of epilepsy. While certain treatments can block epileptogenesis in specific animal models of epilepsy (such as the amygdala kindling model), there are as yet no clinical approaches known to retard or check the progression of epilepsy or prevent its occurrence in human subjects [27, 28].

14.4 MECHANISMS OF ACTION OF AEDS

AEDs protect against seizures through interactions with a variety of cellular targets. The actions on these targets can be categorized into four broad groups: (1) modulation of voltage-gated ion channels (mainly sodium and also calcium channels); (2) effects on GABA systems, including enhancement of synaptic inhibition mediated by GABA~A~ receptors; (3) inhibition of synaptic excitation mediated by ionotropic glutamate receptors; and (4) direct effects on synaptic release machinery [29, 30] (see Table 14.2). The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites. Some seizures, including typical generalized absence seizures, are believed to result from thalamocortical synchronization. AEDs effective in these seizure types interfere with the rhythm-generating mechanisms that underlie the synchronized activity in the thalamocortical circuit. (See Table 14.3 and 14.4 for the molecular targets and therapeutic activities of AEDs.)

### TABLE 14.2 AED Mechanisms

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Modulation of voltage-dependent Na⁺ or Ca²⁺ channels (leading to secondary inhibition of synaptic release, particularly of glutamate, or to inhibition of intrinsic bursting)</td>
</tr>
<tr>
<td>2.</td>
<td>Enhancement of GABA-mediated inhibition or other effects on GABA systems</td>
</tr>
<tr>
<td>3.</td>
<td>Inhibition of synaptic excitation mediated by ionotropic glutamate receptors</td>
</tr>
<tr>
<td>4.</td>
<td>Modulation of synaptic release, particularly of glutamate, through direct actions on release machinery</td>
</tr>
</tbody>
</table>
### TABLE 14.3 Molecular Targets of AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Voltage-Activated Sodium Channels</th>
<th>Voltage-Activated Calcium Channels</th>
<th>GABA System</th>
<th>Ionotropic Glutamate Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominant Sodium (and Calcium) Channel Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>$I_{NaF}$, $I_{NaP}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>$I_{NaF}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>$I_{NaF}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>$I_{NaF}$</td>
<td></td>
<td>$HVA$</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>$I_{NaF}$</td>
<td></td>
<td>$T$ type</td>
<td></td>
</tr>
<tr>
<td><strong>Predominant Calcium Channel Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>$I_{NaP}$</td>
<td></td>
<td>$T$ type</td>
<td></td>
</tr>
<tr>
<td><strong>GABA Systems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>$I_{NaF}$</td>
<td></td>
<td>$GABA_A R$</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>$I_{NaF}$</td>
<td></td>
<td>$GABA-T$</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>$I_{NaF}$</td>
<td></td>
<td>$GABA$ transporter</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>$I_{NaF}$</td>
<td>$HVA$</td>
<td>$GABA_A R$</td>
<td>$NMDA$</td>
</tr>
<tr>
<td>Topiramate</td>
<td>$I_{NaF}$, $I_{NaP}$</td>
<td>$HVA$</td>
<td>$GABA_A R$</td>
<td>$KA/AMPA$</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>$I_{NaF}$</td>
<td>$HVA$</td>
<td>$GABA_A R$</td>
<td>$AMPA$</td>
</tr>
<tr>
<td><strong>Novel Targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>$\alpha\delta$ Protein (calcium channel subunit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>$\alpha\delta$ Protein (calcium channel subunit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>SV2A synaptic vesicle protein</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**: AMPA, $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, $\gamma$-aminobutyric acid; GABA-T, GABA aminotransferase; $GABA_A R$, $GABA_A$ receptor; HVA, high-voltage activated; $I_{NaF}$, fast sodium current; $I_{NaP}$, persistent sodium current; KA, kainate; NMDA, $N$-methyl-$D$-aspartate.

**Source**: Adapted from: [29, 31].
### TABLE 14.4 Selected Therapeutic Activities of Marketed AEDs

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Established and Potential Therapeutic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium (and Calcium) Channel Modulation</strong></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Localization-related epilepsy, GTC seizures</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Localization-related epilepsy, GTC seizures</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Localization-related epilepsy, GTC seizures</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Localization-related epilepsy, GTC seizures, absence, myoclonus (JME), Lennox–Gastaut</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Localization-related epilepsy, GTC seizures, myoclonus (JME), absence, infantile spasms, Lennox–Gastaut</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Primary generalized absence</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: localization-related and secondary generalized</td>
</tr>
<tr>
<td><strong>Mixed Actions</strong></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Localization-related epilepsy, Lennox–Gastaut syndrome</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Localization-related epilepsy, primary GTC seizures, Lennox–Gastaut syndrome, myoclonus (JME)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Localization-related epilepsy, GTC seizures</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence</td>
</tr>
<tr>
<td><strong>GABA Systems</strong></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Localization-related epilepsy, GTC seizures, absence, myoclonus</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Localization-related epilepsy, infantile spasms</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Localization-related epilepsy</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence</td>
</tr>
<tr>
<td><strong>Novel Targets (Possible Direct Effects on Synaptic Release Mechanisms)</strong></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Localization-related epilepsy, myoclonus (JME), absence</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Localization-related epilepsy, GTC</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: absence, myoclonus</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Localization-related epilepsy</td>
</tr>
<tr>
<td><strong>Obscure Targets</strong></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Idiopathic generalized epilepsy (including absence, primary GTC seizures, myoclonic seizures including JME, astatic seizures), localization-related epilepsy, GTC seizures, infantile spasms, neonatal seizures</td>
</tr>
<tr>
<td>ACTH</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td></td>
<td><em>Inactive</em>: all other seizure types</td>
</tr>
</tbody>
</table>

Note: Therapeutic activities are based on results of controlled trials or open-label trials and general acceptance of utility. In many patients with secondary generalized epilepsies such as the Lennox–Gastaut syndrome, even drugs shown to be effective in controlled trials may only reduce seizure frequency to a limited degree.

Abbreviations: GTC, generalized tonic-clonic seizures; JME, juvenile myoclonic epilepsy. ACTH and glucocorticoids are believed to be effective in the treatment of infantile spasms; the mechanism of action is unknown.
14.4.1 Modulation of Voltage-Activated Sodium Channels

Several AEDs are believed to act largely through modulation of the gating of voltage-activated sodium channels, although effects on other targets including voltage-activated calcium channels may play a role in seizure protection. These include phenytoin, lamotrigine, carbamazepine, oxcarbazepine, and zonisamide (Table 14.2). Other AEDs that may act, at least in part, through effects on sodium channels include felbamate, topiramate, and valproate. Sodium channel-blocking AEDs inhibit high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ordinary ongoing neural activity. This accounts for their relatively mild effects on normal brain function. At ordinary hyperpolarized membrane potentials, clinically relevant concentrations of sodium channel-blocking AEDs block sodium channels only weakly. However, upon membrane depolarization, the degree of block markedly increases. Moreover, block accumulates with prolonged or repetitive activation, a property referred to as “use dependence.” Due also to slow onset and recovery of block, normal action potentials, in contrast to the sustained depolarizations of ictal discharges, are relatively unperturbed [32, 32a]. The state-dependent block produced by AEDs that act on voltage-activated sodium channels results from preferential binding of the drugs to inactivated conformations of the channel. These agents act mainly on action potential firing; the drugs do not directly alter excitatory or inhibitory synaptic responses. However, a critical downstream action of AEDs that act on voltage-activated sodium channels may be to reduce action potential–dependent neurotransmitter release, particularly that dependent upon prolonged high-frequency firing as occurs during epileptic discharges [33, 34]. Interestingly, such drugs seem to have a preferential action on glutamate release and only weakly affect GABA release, possibly as a result of differences in excitation–contraction coupling in glutamatergic and GABAergic neurons [35, 36]. Voltage-activated sodium channel block also may reduce the propagation of action potentials from the soma into dendrites and may reduce the dendritic amplification of synaptic potentials [30]. Together, these actions inhibit the spread of epileptiform activity. Blockade of noninactivating sodium currents that arise from alternate gating of the same channels responsible for fast sodium currents and influence initiation and maintenance of epileptiform activity may also contribute to AED effects [37]. Enhanced persistent sodium currents are associated with epilepsy in some forms of the “generalized epilepsy with febrile seizures plus” syndrome [38].

14.4.2 GABA Systems

The GABA system is the second key target for AEDs. Drugs that block GABA_A receptors are well known to induce seizures, and subunit mutations have been associated with inherited epilepsy syndromes [39, 40]. AEDs can interact with GABA systems either through direct effects on postsynaptic GABA receptors or by altering the cellular disposition of GABA. Benzodiazepines are examples of drugs that act on postsynaptic GABA receptors. They are specific for ionotropic GABA_A receptors containing the γ2 subunit and act to allosterically modulate these receptors to increase chloride channel-opening frequency. This effect enhances synaptic inhibition, resulting in a broad-spectrum anticonvulsant effect. Benzodiazepines can
protect against many seizure types in animal models and in humans, but because of
the development of tolerance, they are not generally useful in the chronic treatment
of epilepsy. In most epilepsy syndromes, the specific cellular types that are involved in
the antiseizure activity of benzodiazepines is not known. However, in the case of
absence epilepsy, it is believed that benzodiazepines desynchronize the thalamocor-
tical oscillations underlying generalized spike-wave discharges by specific effects on
$\alpha_3$-containing GABA$_A$ receptors in the thalamic reticular nucleus [41]. Barbiturates,
including phenobarbital, also potentiate GABA$_A$ receptor responses and this is, at
least in part, responsible for their antiseizure activity. Presumably because they are
not specific for $\alpha_3$-containing GABA$_A$ receptors, barbiturates are not active in
absence epilepsy and may even aggravate absence seizures. In contrast to benzodia-
zepines, barbiturates do not appear to increase the frequency of GABA-induced
chloride channel opening but instead increase open time probability [42]. In addition
to effects on GABA$_A$ receptors, barbiturates modulate other ion channel systems,
including calcium and sodium channels, and these actions may contribute to
therapeutic activity [43]. Phenobarbital causes sedation and some degree of cognitive
impairment at clinically effective doses. Tolerance generally develops to these adverse
effects but interestingly not to the anticonvulsant activity [44]. Nevertheless, with-
drawal of phenobarbital can lead to seizure exacerbation, as also occurs with
benzodiazepines [45].

Drugs that alter the disposition of GABA are vigabatrin, which inhibits GABA
metabolism, and tiagabine, which inhibits GABA uptake. Vigabatrin (γ-vinyl
GABA) is an irreversible suicide inhibitor of GABA-T, the main metabolic enzyme
for GABA, which catalyzes the transfer of an amino group from GABA to pyruvate,
forming alanine and succinate semialdehyde [46]. Administration of vigabatrin leads
to large elevations in brain GABA levels in animals [47] and humans [48]. In
addition, the drug causes a dose-dependent increase in cerebrospinal GABA in
human subjects with epilepsy, without affecting the levels of other neurotransmitters,
including monoamines [49, 50]. Although GABA-T is present in both neurons and
glia [51], the increase in brain GABA levels is predominantly due to inhibition of
GABA-T in neurons [52]. While it seems reasonable that these increases in brain
GABA would enhance inhibitory tone, in fact, vigabatrin does not potentiuate
synaptic inhibition [53], and this is consistent with its lack of sedative effects.
However, the antiseizure effects of vigabatrin are hard to explain [54]. One possibility
is that vigabatrin increases tonic current resulting from the action of ambient GABA
on extrasynaptic GABA$_A$ receptors [54–56]. Vigabatrin may cause elevated extra-
cellular GABA levels as a result of efflux of GABA from neurons via reversal of
GABA transporters. The enhanced activation of extrasynaptic GABA$_A$ receptors
produced by the elevated extracellular GABA could be the critical factor in the
anticonvulsant activity of the drug. An alternate hypothesis is that vigabatrin
prevents the fading of GABA responses during repetitive activation of inhibitory
pathways through reduced function of release-regulating presynaptic GABA$_B$
receptors [57]. Such fading is believed to be an important factor that permits focal
epileptiform activity to develop into a full-blown seizure.

In contrast to vigabatrin, the GABA transporter blocker tiagabine [58] does
elevate synaptic levels of GABA by inhibiting transport of GABA into nerve
terminals and glia, resulting in increased synaptic inhibition [59]. In line with these
effects on synaptic inhibition, tiagabine does have sedative side effects.
14.4.3 T-Type Calcium Channels

Low-voltage-activated (T-type) calcium channels play a role in the intrinsic thalamic oscillations that underlie generalized absence seizures [60, 61]. Ethosuximide, which is highly efficacious in the treatment of absence seizures (but not other seizure types) seems to act by inhibition of T-type calcium channels in thalamic neurons [62, 63]. Zonisamide, in addition to effects on voltage-activated sodium channels (Table 14.3), may also block T-type calcium channels [64], thus accounting for its efficacy in absence epilepsy (Table 14.4).

14.4.4 Ionotropic Glutamate Receptors

Ionotropic glutamate receptor–gated cation channels are responsible for most CNS fast excitatory neurotransmission [65]. Selective blockade of NMDA, AMPA, and KA subtypes protects against seizures in animal models [66, 67]. None of the marketed AEDs specifically and uniquely targets ionotropic glutamate receptors. However, several AEDs, including felbamate and topiramate, may, at least in part, act through effects on these receptors (see below).

14.4.5 Calcium Channel $\alpha_2\delta$ Subunit

Gabapentin and pregabalin are 3-substituted analogs of GABA that were originally synthesized with the intent that they would act on GABA systems. However, neither drug is believed to function through an influence on GABA metabolism or on GABA receptors as do other AEDs that target GABAergic neurotransmission. Rather, both gabapentin and pregabalin are high-affinity ligands for calcium channel $\alpha_2\delta$ subunits. The $\alpha_2\delta$ represents a family of four related proteins [molecular weight (MW) $\sim$ 125 kD] encoded by separate genes [68, 69]. Only $\alpha_2\delta_1$ and $\alpha_2\delta_2$ bind gabapentin and pregabalin with high affinity [70]. The $\alpha_2\delta_1$ is expressed ubiquitously in the body whereas $\alpha_2\delta_2$ is mainly expressed in the brain and heart. $\alpha_2\delta_1$ and $\alpha_2\delta_2$ are believed to serve as auxiliary subunits of voltage-activated calcium channels, although it is possible that they have other functions as well. Both proteins form complexes with many calcium channel types (represented by different $\alpha_1$ isoforms), allosterically enhancing current amplitude and also promoting channel trafficking to the membrane [71]. The mouse mutant duckey, which is associated with mutations in the $\alpha_2\delta_2$ gene, exhibits spontaneous spike-wave seizures [72]. Similarly, targeted deletion of the $\alpha_2\delta_2$ gene results in enhanced seizure susceptibility [73]. These mouse models confirm a role for $\alpha_2\delta_2$ in the regulation of seizure susceptibility.

The precise way in which binding of gabapentin and pregabalin to $\alpha_2\delta_1$ and $\alpha_2\delta_2$ leads to protection against seizures is not fully understood, although there is likely to be an effect on synaptic release of neurotransmitters, including glutamate. Numerous studies have examined the effects of gabapentin or pregabalin on voltage-gated calcium channel function. There are several reports that the drugs reduce calcium current in neuronal cell bodies [74–76]. However, in other studies, gabapentin was inactive [71]. There is, however, agreement that gabapentin and pregabalin reduce calcium influx into presynaptic nerve terminals [77, 78]. This would be expected to reduce neurotransmitter release, and, in fact, there are reports that the release of several neurotransmitters, including glutamate, is reduced by both drugs [79, 79a,
Recently, several studies have indicated that not only calcium-dependent release of neurotransmitters but also spontaneous, calcium-independent release of individual transmitter vesicles from glutamate synapses is reduced by treatment with gabapentin or pregabalin (see [30]). These results suggest that the actions of $\alpha_2$-d ligands to reduce neurotransmitter release may not require inhibition of calcium influx and therefore may be mediated by an interaction of $\alpha_2$-d (or the calcium channel complex containing $\alpha_2$-d) with synaptic proteins that are involved in the release or trafficking of synaptic vesicles.

**14.4.6 Synaptic Vesicle Protein SV2A**

The AED levetiracetam is approved for the treatment of localization-related epilepsy and is probably also effective for juvenile myoclonic epilepsy and generalized absence epilepsy (Table 14.4). Levetiracetam has a spectrum of activity in animal models that differs from other agents, and until recently its mechanism of action was obscure [80, 81, 81a]. However, emerging evidence indicates that levetiracetam, like gabapentin and pregabalin, may act through a novel target linked to the synaptic release machinery. In 1995, a saturable and stereoselective specific binding site for [3H]levetiracetam was describe in brain membranes [82]. The binding site was subsequently identified as the ubiquitous synaptic vesicle protein SV2A [83]. Thus, levetiracetam has a novel target that is distinct from that of other AEDs, and it is the first AED that has been demonstrated to bind directly to the synaptic vesicles. SV2A seems to interact with synaptotagmin, which is believed to be the calcium sensor in exocytosis [84]. It is now recognized that SV2A is a member of a small family of homologous proteins that also includes SV2B and SV2C, but only SV2A — the most ubiquitous form — binds levetiracetam. Studies with mice in which the SV2 proteins have been deleted by gene targeting are consistent with a possible role of SV2A in regulating seizure susceptibility, but they have not yet provided insight into the function of SV2A and how levetiracetam binding confers seizure protection. In SV2A knockout mice, brain morphology and indeed the morphology of synapses are normal [85, 86]. However, SV2A knockout mice experience severe seizures. The SV2 proteins do not appear to be required for synaptic transmission or for the uptake or storage of neurotransmitters, although they may play a subtle role in the release process during repetitive synaptic activation (as occurs during seizure activity) by regulating nerve terminal calcium dynamics [86]. Given the way binding to SV2A results in seizure protection, it is likely that there is an influence on synaptic release, which is in accord with the unifying concept that the ultimate action of many AEDs, whatever their molecular targets, is to modulate neurotransmitter release.

**14.4.7 AEDs with Mixed Actions**

**14.4.7.1 Felbamate.** Felbamate has a broad spectrum of activity, including efficacy in the treatment of the Lennox–Gastaut syndrome (Table 14.4). Felbamate probably acts through several target interactions, including actions on GABA$_A$ and NMDA receptors. Drugs that block NMDA receptors have powerful anticonvulsant activity in animal models, although it is less clear that such agents are useful in the treatment of human epilepsies [27]. Nevertheless, felbamate is the only AED that targets NMDA receptors at therapeutic concentrations. Structurally, felbamate is an analog
of the sedative–hypnotic drug meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate). Like meprobamate, felbamate potentiates GABA responses via an interaction with a site on the GABA_A receptor that is distinct from the benzodiazepine recognition site [87, 88]. In addition, felbamate blocks NMDA receptor–mediated synaptic responses [89] and inhibits NMDA receptor currents in cultured neurons [87, 90]. On the basis of whole-cell and single-channel recordings, Subramaniam et al. [90] concluded that felbamate acts both by a channel-blocking mechanism and by distinct effects on channel gating. Details of the effects on gating have been defined by Kuo et al. [91], who found that felbamate blocks the late sustained phase of NMDA receptor responses more readily than the initial onset of the response, which may confer selectivity for seizure activity, since prolonged pathological activations would be suppressed more strongly than more rapid, normal NMDA responses. In addition, the block of NMDA receptor responses was greater with high concentrations of NMDA, another factor that would allow the drug to selectively block seizure discharges associated with strong activation of NMDA receptors. Studies with recombinant NMDA receptor subunit combinations have indicated that felbamate selectively blocks NMDA receptors composed of NR2B subunits at lower concentrations than other subunit combinations [92, 93, 93a]. Since NR2B subunits have a restricted distribution in the adult (mainly to the forebrain), this selectivity could contribute to the relatively low neurobehavioral toxicity of felbamate in relation to other NMDA receptor antagonists. Moreover, the subunit selectivity could also account for the clinical utility of felbamate in seizure disorders affecting the immature brain, such as the Lennox–Gastaut syndrome, since NR2B subunits are more abundant in the developing brain.

14.4.7.2 Topiramate. Topiramate is approved for the treatment of localization-related epilepsy, primary GTC seizures, and seizures associated with the Lennox–Gastaut syndrome; it is probably also effective for myoclonic seizures in juvenile myoclonic epilepsy and generalized absence epilepsy (Table 14.4). Several cellular mechanisms have been proposed to underlie the therapeutic activity of topiramate: (1) use-dependent attenuation of voltage-activated sodium currents [94, 95]; (2) inhibition of high-voltage-activated calcium channels [96]; (3) potentiation of GABA_A receptor–mediated currents [97–100]; (4) inhibition of AMPA/KA receptors [101–103]; (5) inhibition of types II and IV carbonic anhydrase isoenzymes [104]; and (6) activation of a steady potassium current [105]. The effects on sodium channels occur at relatively low, therapeutically relevant concentrations and are similar to the effects of other sodium channel-blocking anticonvulsants, particularly phenytoin. In addition to effects on fast sodium currents, topiramate, like phenytoin, blocks persistent sodium currents at low concentrations. Because persistent sodium current may contribute to the initiation and maintenance of epileptiform activity, this action could represent an important factor in the anticonvulsant properties of topiramate. The inhibitory action of topiramate on high-voltage-activated calcium current is of uncertain relevance, since the drug was specific for L-type currents [96] and L-type calcium channel blockers are not effective as anticonvulsants.

Effects of topiramate on GABA_A receptors could contribute to the broad spectrum of activity of topiramate. Topiramate is not active in animal models, such as the pentylenetetrazol test, that are typically sensitive to drugs that positively modulate GABA_A receptors. Nevertheless, the drug does have activity in an absence
epilepsy model and can affect pentylentetrazol threshold, which is consistent with effects on GABA<sub>A</sub> receptors. The activity of topiramate as a modulator of GABA<sub>A</sub> receptors varies in different in vitro preparations [101, 106]. Recent evidence indicates that this variability may result from subunit selectivity. In particular, the type of β-subunit type (β<sub>1</sub> versus β<sub>2</sub> or β<sub>3</sub>) may strongly influence how topiramate acts on GABA<sub>A</sub> receptors.

The activity of topiramate in animal models is compatible with effects on ionotropic glutamate receptors, including NMDA and AMPA/KA receptors. There is no evidence that topiramate blocks NMDA receptors [101]. However, in cultured neurons, it does inhibit responses to KA, an agonist of AMPA and KA receptors [102]. Recently, topiramate was found to be a more potent and efficacious inhibitor of GluR5 KA receptor currents in basolateral amygdala principal neurons than of AMPA receptor currents [106]. AMPA receptors are crucial for excitatory synaptic transmission throughout the CNS, and drugs that substantially block AMPA receptors produce dramatic neurobehavioral impairment [107]. Thus, the finding that topiramate is weak and has low efficacy as an AMPA receptor agonist corresponds with the clinical observation that the drug is reasonably well tolerated (see Table 14.5 for side effects). KA receptors represent a new potential anticonvulsant drug target [108]. Because of their limited distribution, blockade of GluR5 KA receptors is not expected to be associated with the side effects that would occur with inhibition of AMPA receptors. The inhibitory action of topiramate on GluR5 KA receptors develops slowly, suggesting that it acts indirectly (does not bind directly to the receptor–channel complex). Recently, it has been found that topiramate inhibits phosphorylation of serine 845 of the AMPA receptor GluR1 subunit [109], suggesting that the effect of the drug on AMPA and perhaps KA receptors is due to an alteration in the phosphorylation state of the protein.

The relevance of the GluR5 KA receptor blocking activity of topiramate was confirmed in in vivo experiments in mice [110]. In addition to effects on GluR5 KA receptors, topiramate may also affect the more abundant GluR6-containing KA receptors.

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because cross-tolerance to the anticonvulsant activity of topiramate does not occur with the classical carbonic anhydrase inhibitor acetazolamide in mice [111]. However, evidence supporting a role for carbonic anhydrase inhibition in the action of topiramate has come from recent studies of GABA<sub>A</sub> receptor–mediated depolarizing responses, which can be elicited by high-frequency stimulation of GABA synapses [105]. Such depolarizing GABA responses may promote the generation of seizure discharges. The efflux of intracellular bicarbonate formed by carbonic anhydrase is believed to contribute to depolarizing GABA responses. Topiramate at clinically relevant concentrations strongly inhibited depolarizing GABA responses without affecting hyperpolarizing GABA-mediated inhibitory postsynaptic potentials. This effect is assumed to be due to due to carbonic anhydrase inhibition as it was mimicked by acetazolamide.

The broad-spectrum anticonvulsant activity of topiramate is likely to result from mixed effects on several target sites, including voltage-activated sodium channels, KA receptors, GABA<sub>A</sub> receptor subtypes, and possibly carbonic anhydrase isoenzymes. The effects on ion channels are unlikely to occur through direct modulation of channel gating as is the mode of action of other AEDs that target the ion channel.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Seizure Syndromes</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Maximum Daily Dose</th>
<th>Neurologic Toxicity</th>
<th>Systemic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>LRE</td>
<td>30 mg</td>
<td>Weekly</td>
<td>4 mg/kg</td>
<td>Sedation, cognitive, behavioral impairment</td>
<td>Hypocalcemia, hypersensitivity</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>LRE</td>
<td>300</td>
<td>Loading</td>
<td>600 mg</td>
<td>Cerebellar impairment</td>
<td>Allergic, hematologic, endocrine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>LRE</td>
<td>100 mg</td>
<td>Weekly</td>
<td>2000 mg</td>
<td>Dizziness, diplopia</td>
<td>Allergic, hematologic, endocrine</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>LRE</td>
<td>150 mg</td>
<td>2–4 days</td>
<td>2400 mg</td>
<td>Headache, dizziness, hyponatremia, rash</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>LRE, SGE, PGE</td>
<td>25 mg</td>
<td>Weekly</td>
<td>1000 mg</td>
<td>Dizziness, diplopia, ataxia</td>
<td>Allergic</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>LRE</td>
<td>5 mg/kg</td>
<td>Weekly</td>
<td>45 mg/kg</td>
<td>Dizziness, psychiatric, cognitive, behavioral impairment</td>
<td>Minimal</td>
</tr>
<tr>
<td>Topiramate</td>
<td>LRE, SGE</td>
<td>25 mg</td>
<td>Weekly</td>
<td>800 mg</td>
<td>Cognitive, behavioral impairment</td>
<td>Renal stones, glaucoma</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>LRE</td>
<td>600 mg</td>
<td>2–4 days</td>
<td>5400 mg</td>
<td>Dizziness, ataxia</td>
<td>Minimal</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>LRE, SGE</td>
<td>100 mg</td>
<td>Biweekly</td>
<td>600 mg</td>
<td>Sedation, psychomotor slowing</td>
<td>Renal stones, rare rash</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>LRE</td>
<td>4 mg</td>
<td>Weekly</td>
<td>64 mg</td>
<td>Sedation, depression</td>
<td>Low</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>LRE, SGE, PGE</td>
<td>10 mg/kg</td>
<td>Weekly</td>
<td>100 mg/kg</td>
<td>Sleepiness, tremor, dizziness</td>
<td>GI, hepatic, endocrine</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>PGE</td>
<td>5 mg/kg</td>
<td>Weekly</td>
<td>40 mg/kg</td>
<td>Sedation, dizziness, behavioral impairment</td>
<td>GI, hypersensitivity</td>
</tr>
<tr>
<td>Felbamate</td>
<td>LRE, SGE</td>
<td>15 mg/kg</td>
<td>2–4 days</td>
<td>45 mg/kg</td>
<td>Insomnia, headache</td>
<td>Aplastic anemia, hepatic failure</td>
</tr>
</tbody>
</table>

**Abbreviations:** LRE, localization-related epilepsy; PGE, primary generalized epilepsy; SGE, secondary generalized epilepsy; GI, gastrointestinal.

Rather, the pharmacological actions of topiramate seem to be mediated indirectly, possibly through effects on channel phosphorylation.

14.5 RELATION OF AED MECHANISM TO CLINICAL EFFICACY

AEDs that modulate voltage-activated sodium channels, such as phenytoin and carbamazepine, are generally effective in the treatment of localization-related epilepsy and generalized tonic–clonic seizures. However, lamotrigine, another sodium channel modulator, is effective in absence epilepsy and probably other forms of primary generalized epilepsy. The basis for the broader spectrum of activity of lamotrigine is unknown but could relate to actions of the drug on voltage-activated calcium channels [29]. AEDs that act specifically on the GABA system through effects on the disposition of GABA, such as vigabatrin and tiagabine, are generally only effective for localization-related epilepsy. In contrast to vigabatrin and tiagabine, agents that act as positive modulators of GABA$_A$ receptors, such as benzodiazepines, have among the broadest spectrum of efficacy of any AEDs. Thus, the specific way in which an AED acts on its target system in the brain dramatically alters its spectrum of activity. Every drug except ethosuximide, across a wide range of potential mechanisms, provides some benefit for patients with localization-related epilepsy. This is not surprising since the principal registrational clinical trials confirming the efficacy of these agents were restricted to patients with localization-related seizures. Ethosuximide is unique in having a very narrow efficacy range, largely restricted to primary generalized epilepsies and possibly only absence epilepsy. As yet, there is insufficient information on which to derive general principles as to the clinical spectrum of activity of modulators of $\alpha_2\delta$, the target for gabapentin and pregabalin, and SV2A, the target of levetiracetam. However, it is interesting that levetiracetam does appear to have a unique spectrum of activity, with efficacy not only in localization-related epilepsy but also in idiopathic myoclonic seizures (as in the juvenile myoclonic epilepsy syndrome) and probably also primary generalized absence epilepsy. In contrast, gabapentin and pregabalin are probably mainly useful in localization-related epilepsy and generalized tonic–clonic seizures. Drugs that seem to act by mixed or complex mechanisms, such as valproate, felbamate, and topiramate, may have broader clinical spectrums. Valproate is the drug of first choice for the treatment of a wide range of idiopathic generalized epilepsies and secondary generalized epilepsies and is also effective in the treatment of localization-related epilepsy. While its mechanism of action is obscure, it has been proposed that effects on the synthesis and turnover of GABA may be of importance [30]. Both felbamate and topiramate are effective in the treatment of localization-related epilepsy. In addition, felbamate has activity in the Lennox–Gastaut syndrome, one of the catastrophic epilepsies of childhood [112]. Topiramate is probably effective in primary generalized tonic–clonic seizures [113] and in the Lennox–Gastaut syndrome [114].

14.6 DEVELOPMENT AND TESTING OF AEDS

The first effective AEDs, sodium bromide in 1857 and phenobarbital in 1912, were identified because of their sedative properties and subsequently introduced into
epilepsy therapy. Modifications of the barbiturate substrate led in the 1930s to
diphenylhydantoin (phenytoin), the first nonsedative AED. Phenytoin was identified
as a potential AED through testing in a cat electroshock seizure model. Most
subsequent AEDs have been found through screening in a battery of animal seizure
models [115]. In a few cases, notably vigabatrin and tiagabine, which were designed
to target the GABA system, a rational approach to drug development was used. The
Antiepileptic Drug Development Program sponsored by the National Institute of
Neurological Disorders and Stroke has aided AED discovery programs in industry
and academia [116, 117, 117a].

Clinical development of older AEDs, including phenytoin, ethosuximide, carbama-
zepine, and valproate, were based on less formal standards than apply today [118].
Beginning in the 1990s, approval of new drugs has been based on large, well-
controlled multicenter trials. These trials have demonstrated efficacy mainly in the
treatment of localization-related epilepsy. However, it has been noted that such trials
do not necessarily demonstrate the overall effectiveness of drugs in clinical practice,
which depends on a wide range of factors including ease of use, long-term toxicity,
need for clinical monitoring, and cost [119]. Indeed, our knowledge of AED efficacy
is related to the peculiarities of their clinical evaluation. Due to the danger of
increased seizure frequency in untreated patients with epilepsy, it has been very
difficult to devise trial designs in which an experimental drug is compared with
placebo. In consequence, most studies in the United States use an “add-on” design in
which either experimental drug or placebo is added to stable standard therapy [120–
122]. A drug successful in such a trial is approved for use as “adjunctive” therapy.

One strategy to achieve approval for “monotherapy” involves inpatient drug
withdrawal (standard during video-EEG monitoring to identify seizure foci in
patients being considered for surgery) followed by addition of experimental drug
or placebo [123]. This process is expensive, may have relatively higher risks of
increased seizures, and does not necessarily mirror conventional clinical treatment
due to the effects of baseline AED withdrawal. Dose–response trials have compared
high and low doses of the same AED or a low dose of a standard drug (hoping to
prevent GTCS but show efficacy of the experimental agent for CPS). However, these
approaches, designed to meet regulatory considerations, do not mimic clinical
practice and may raise ethical issues [124].

“Outpatient withdrawal to monotherapy” with a drug already approved for
adjunctive therapy is another approach that approximates clinical practice in which
patients well controlled on two AEDs are often given the option to try to eliminate
one of them [125]. Parallel design trials comparing experimental agents with an
established drug in patients with new-onset epilepsy have been performed, usually
involving agents for which a fair amount of preliminary efficacy data exist [126].
These may suffer from the limitation that equivalence in effect on seizure frequency
between “new” and “established” AEDs can be interpreted as evidence for equal
effectiveness or equal ineffectiveness.

Most antiepileptic drugs have been tested in adult patients with localization-
related, usually temporal lobe, epilepsy. This group makes up the largest number of
subjects with uncontrolled epilepsy, and their seizures are relatively easier to control
than the atonic or atypical absence seizures of patients with secondary generalized
epilepsies. Consequently, there are fewer effective agents for the latter, who suffer as
well from more severe neurological disorders. Drugs are mainly tested in adults first
in order to reduce the risk of injury to children, but most patients have epilepsy onset in childhood, and it is important to try to control their seizures as early as possible to prevent adverse social and educational as well as developmental effects.

Unfortunately, then, epilepsy therapy has only a limited “evidence base.” Some investigators have suggested that, given the limitations of the AED development process, “patient preference” may be as reliable a guide in clinical practice as the results of controlled trials [127].

14.7 CLINICAL MARKERS TO PREDICT AED EFFICACY

Ideally, epilepsy treatment should be guided by an “evidence-based” approach, depending on the results of randomized controlled trials (RCTs). Evidence of AED efficacy and clinical decision making should be based on class 1 evidence from controlled, blinded, randomized clinical trials. However, the difficulties and expense of standard clinical AED trials have led to interest in development of surrogate markers of both epilepsy and epileptogenesis. Imaging studies such as PET and MRI are being used to track the effects of pharmacological and surgical treatment in multiple sclerosis and Parkinson’s disease.

None of several potential surrogate markers has been accepted by regulatory agencies or the epilepsy “community” as a reliable indicator of AED efficacy or toxicity. Drug effects on EEG have not been shown to correlate with clinical efficacy, except in patients with primary generalized absence. Transcranial magnetic stimulation (TMS) can be used to evaluate drug effects on cortical excitability. Alterations in TMS measures correlate with AED blood levels, and the specific effects obtained may differ depending upon the AED mechanism of action, but effects on TMS parameters have not yet been shown to reliably reflect seizure frequency reduction [128, 129].

Magnetic resonance spectroscopy has shown that several AEDs increase brain GABA or homocarnosine levels and that the increase may correlate with seizure control [46, 130]. Studies with PET have shown that AEDs associated with cognitive impairment, such as barbiturates, decrease glucose metabolism more than others and that vigabatrin reduces central benzodiazepine receptor binding [131].

Approximately 5% of patients with epilepsy exhibit photosensitivity in which a generalized epileptiform response is observed in the EEG with intermittent photic stimulation (IPS). In these subjects, epileptiform discharges can be reliably evoked in the laboratory at any time by IPS. It has been demonstrated that single acute doses of various AEDs suppress photosensitivity, whereas drugs that do not have antiepileptic actions, even if they produce marked drowsiness, do not [132]. This approach has frequently been used in the early clinical evaluation of potential AEDs to provide an early indication of clinical efficacy and to assess duration of action [133].

14.8 LIMITATIONS OF DRUG TRIALS FOR DETECTING IDIOSYNCRATIC TOXICITIES

Even large-scale randomized controlled clinical trial programs accrue only a few thousand patients at most. Inevitably, rare but serious side effects will not appear until AEDs (or indeed any drugs) come into widespread use. For example, felbamate,
a drug effective for several seizure types that had the advantage of not causing sedation or other manifestations of CNS depression, turned out to cause aplastic anemia at a rate of between 27 and 209 per million users, compared with the general population rate of 2 per million per year [134]. Vigabatrin was found to cause visual field constriction due to retinal toxicity and topiramate acute closed-angle glaucoma [135]. Vigabatrin was never approved in the United States, and its use in Europe has declined. The use of felbamate is restricted to patients that are refractory to other AEDs.

14.9 USING ANTIEPILEPTIC DRUGS

The choice of an AED involves evaluation of its relative advantages, including efficacy, ease of use, and lack of drug interactions, and disadvantages, including toxicity and cost. Table 14.5 shows the range of uses, dosing, and most common or severe side effects for selected AEDs. It is noteworthy that almost all AEDs may cause some mild sedation, to which patients often develop tolerance over time. Table 14.6 provides pharmacokinetic information. Protein binding, half-life, and other parameters shown may be affected by age, drug interactions, pregnancy, and systemic disease. Interactions with other AEDs and therapeutic agents appear to be most extensive for AEDs that induce hepatic enzymes, such as carbamazepine, phenytoin, and phenobarbital. These AEDs can affect the levels of many drug classes, including oral contraceptives, steroids, and anticoagulants. For most AEDs, effective doses are higher on a milligram-per-kilogram basis for children (except newborns) than adults. AED doses and levels should be taken only as guides, not rigid rules. Recent studies have challenged the value of the routine monitoring of AED plasma levels, particularly in large clinical populations when the newer AEDs are being used [136].

14.9.1 Generalized Absence Epilepsy

In the United States, ethosuximide is the most widely used drug. In Europe, valproic acid has become more popular, particularly in the salt form (divalprox sodium), which has less gastrointestinal toxicity. However, increasing recognition of adverse endocrine effects and the risk of teratogenicity (particularly when doses of more than 1000 mg per day are given) [137], have led to increased use of alternatives such as lamotrigine. The available data do not allow therapeutic distinctions among these three agents [138].

14.9.2 Localization-Related Epilepsy

For patients with localization-related epilepsy, it is reasonable to start therapy with any of several AEDs. Phenobarbital is the most widely used AED worldwide due to its low cost. The long half-life is another advantage, allowing once-daily dosing, which increases compliance. Adverse cognitive effects have reduced use in higher income countries. Phenobarbital is not effective in generalized absence epilepsy and secondary generalized epilepsies, such as the Lennox–Gastaut syndrome. In countries where cost is not an overriding consideration, carbamazepine is probably the most frequently used drug for localization-related epilepsy. Moreover, carbamazepine has become the
<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Plasma Concentration (h)</th>
<th>Protein Binding (%)</th>
<th>Clearance</th>
<th>$T_{1/2}$ (h)</th>
<th>Drug Interactions</th>
<th>Therapeutic Level (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>1–3</td>
<td>55%</td>
<td>Hepatic</td>
<td>15–60</td>
<td>AEDs</td>
<td>10–60</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2–3 approx. dose</td>
<td>0</td>
<td>Renal</td>
<td>6–7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Minimal</td>
<td>40–120</td>
</tr>
<tr>
<td>Tagabine</td>
<td>1–2</td>
<td>96</td>
<td>CYP3A</td>
<td>5–8</td>
<td>AEDs</td>
<td>—</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>1–2</td>
<td>0</td>
<td>Mixed</td>
<td>5–7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2–4</td>
<td>15</td>
<td>Mixed</td>
<td>18–23</td>
<td>Lithium, OCs, some AEDs</td>
<td>10–60</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>1–2</td>
<td>40</td>
<td>Non–CYP mediated</td>
<td>10–12 (MHD metabolite)</td>
<td>AEDs; oral contraceptives</td>
<td>50–140 (MHD)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1–4</td>
<td>40–55</td>
<td>Hepatic</td>
<td>80–130</td>
<td>Extensive</td>
<td>50–130</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2–6</td>
<td>90</td>
<td>Hepatic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Extensive</td>
<td>40–80</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Slow, variable</td>
<td>70–75</td>
<td>Hepatic</td>
<td>18–55&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Extensive</td>
<td>15–45</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1–2</td>
<td>0</td>
<td>Renal</td>
<td>6–10</td>
<td>Minimal</td>
<td>—</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>3–4</td>
<td>40–60</td>
<td>CYP3A</td>
<td>50–60</td>
<td>Extensive</td>
<td>35–200</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>1–2</td>
<td>90&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Hepatic</td>
<td>10–15</td>
<td>AEDs</td>
<td>300–600</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>3–5</td>
<td>0</td>
<td>Hepatic</td>
<td>30–60</td>
<td>AEDs</td>
<td>300–600</td>
</tr>
</tbody>
</table>

**Note:** MHD, the active 10-monohydroxy metabolite of oxcarbazepine.


<sup>a</sup>Uncertain clinical relevance.

<sup>b</sup>Nonlinear.

<sup>c</sup>Single dose healthy subjects.

<sup>d</sup>Patients on chronic therapy.

<sup>e</sup>Concentration dependent.
“standard of comparison” in many parallel design AED trials, used most often for patients with new-onset seizures [121, 122]. Carbamazepine induces its own metabolism, so doses may have to be increased after several weeks of therapy, and the drug has to be taken three or four times a day. There are several extended-release forms of carbamazepine available, allowing twice-daily dosing (of the same total amount), which can increase compliance. In a large multicenter, randomized, controlled trial, carbamazepine and phenytoin were superior to phenobarbital and primidone (now rarely used), but due to lower toxicity, not higher efficacy [139]. Phenytoin now is used less frequently than in the past, particularly in Europe, because it commonly causes cosmetic side effects with chronic use (hypertrichosis, gingival hypertrophy, and coarsening of the facial features) and has also been associated with various other chronic toxicities, including cerebellar degeneration, peripheral neuropathy, and folic acid and vitamin D deficiency with osteomalacia.

In the last decade, 10 new AEDs have been approved for marketing. Although comparative data are limited, the parallel treatment comparisons which have been carried out to date have for the most part shown approximate therapeutic equivalence among currently available agents in patients with new-onset localization-related epilepsy [121, 122]. However, in one study carbamazepine seemed to be more efficacious than gabapentin, but at the price of increased side effects. In this parallel group comparison, patients on 600 mg of carbamazepine were more likely to drop out due to toxicity but less likely due to seizures than patients on 900 mg of gabapentin [126]. The overall study completion rate was equal for the two drugs. Even if it is difficult to discern differences in efficacy among the newer agents for the treatment of localization-related epilepsy, each of the new drugs has unique characteristics that may be more important for one patient than another. Such characteristics include propensity to drug interactions, dosing convenience, dose-related side-effect spectrum, and cost. For example, lamotrigine may have less overall toxicity than carbamazepine [140]. However, lamotrigine is associated with a high incidence of skin rashes that rarely may progress to Stevens–Johnson syndrome or toxic epidermal necrolysis. In randomized trials topiramate had more cognitive toxicity than either gabapentin or lamotrigine but also is associated with weight loss and has some efficacy against headache, experienced by many patients with epilepsy [141].

Barbiturates and benzodiazepines both cause sedation and some degree of cognitive impairment at clinically effective doses. Tolerance develops to the latter but not the former during chronic therapy. Although important for treatment of status epilepticus, benzodiazepines have little role in chronic seizure treatment. Phenobarbital, in contrast, due to its low cost, is the most widely used AED in the world and the only agent practical for addressing the enormous treatment gap in low-income countries.

14.9.3 Combination Therapy

If the first AED used is ineffective, clinicians will generally add a second, which can result in improved seizure control. However, only very rarely do combinations of more than two AEDs further increase seizure control [20, 139]. Moreover, patients with localization-related epilepsy, particularly those with mesial temporal sclerosis, are unlikely to respond to any AED if they have failed combination therapy with two
effective drugs. For these patients, alternative approaches such as surgery should be considered. So far, the approach of choosing drugs with two different putative mechanisms of action, although seemingly rational, has not been shown to lead to better seizure control. Nevertheless, there are several important considerations in choosing AED combinations. The potential for drug interactions needs to be taken into account. Several important drugs, such as phenobarbital, phenytoin, and carbamazepine, induce hepatic cytochrome P450 drug-metabolizing enzymes, which can decrease levels not only of other AEDs but also of other medications such as oral contraceptives, anticoagulants, thyroid hormone, as well as vitamin D levels. It is important to give patients taking AEDs calcium and vitamin D supplements. Women particularly are at increased risk for osteoporosis and fractures [142].

It may be helpful to avoid drugs with overlapping side effects, such as two agents that both cause sleepiness, nystagmus, or ataxia. For example, phenytoin and carbamazepine, previously a popular combination, is now used less frequently. The increased rate of side effects reported when patients are taking AED combinations is greater than can be explained by purely additive effects. It may be due to alterations in levels of the original AED or increased production of toxic metabolites.

14.9.4 Secondary Generalized Epilepsies

The treatment of patients with secondary generalized epilepsies such as Lennox–Gastaut remains unsatisfactory. Valproic acid often is the first drug tried. Several others, including felbamate, lamotrigine, and topiramate, have been found to have statistically significant, although limited, efficacy [143a]. The ketogenic diet has been proposed as alternative therapy, but no controlled data on its effects have been reported. For patients with frequent falls and injuries, corpus callosotomy can be considered, although it is a complex procedure with palliative results at best.

Infantile spasms are a particularly severe form of epilepsy, which in about 50% of patients is due to a metabolic brain disorder or tuberous sclerosis [144]. The most common initial therapy in the United States is ACTH, supplemented by valproic acid, lamotrigine, topiramate, and zonisamide. Vigabatrin, not available in the United States, has been reported to be effective for infantile spasms, particularly in patients with tuberous sclerosis, in open-label studies. A recent controlled trial, however, found that vigabatrin was inferior to either ACTH or corticosteroids when seizure outcome was compared at 14 days after starting treatment [145]. Moreover, because it is difficult to monitor the development of retinal toxicity of vigabatrin in infants, treatment with ACTH continues to be the initial approach of choice.

14.10 ISSUES FOR SPECIAL POPULATIONS

Some AEDs may have side effects that affect women more than men. Valproic acid, for example, has been associated with polycystic ovarian syndrome and secondary amenorrhea [146]. The hepatic enzyme inducers can reduce the efficacy of oral contraceptives and lead to unwanted pregnancy; doses may have to be increased. Phenytoin may lead to hirsuitism, which is a particular concern for women.

AED teratogenicity often is a concern [147]. All AEDs have teratogenic potential, but reliable risk data are limited. Older drugs such as phenobarbital and phenytoin
have been associated with a variety of fetal malformations, often deriving from studies in which drugs were used in combination. Carbamazepine has been associated with neural tube defects in some studies, although the risk is uncertain. For valproic acid, however, the data show clear increased risk, particularly when doses of greater than 1000 mg per day are used [137]. So far, there are no definite reports of malformations associated with the newer AEDs such as lamotrigine, leviteracetam, or topiramate, but exposures are more limited.

The risk of teratogenicity has to be balanced against the adverse effects of seizures on the fetus. Generally, if a patient who is well controlled on an AED regimen becomes pregnant, AED therapy should be continued and it is not advisable to switch agents. Even in the case of valproic acid, the main period of risk may have passed before the patient realizes she is pregnant. It is important to measure AED levels during pregnancy, as increased fluid volume may lead to decreased plasma levels and loss of control.

Infants usually have decreased AED clearance, but older children need higher drug levels on a milligram-per-kilogram basis. Elderly patients generally have reduced AED clearance and should be given lower drug doses. They are more sensitive to pharmacodynamic effects as well, particularly cognitive toxicity. Some side effects, such as loss of balance, may be more serious in the elderly, leading to falls that can cause fractures. Drug interactions may be a particular concern, since elderly patients may be taking drugs for other medical conditions. In a recent study of patients over 60 with new-onset epilepsy, 150 mg of lamotrigine per day was better tolerated than 600 mg of carbamazepine, with no difference in seizure control [148].

14.11 DRUG-RESISTANT EPILEPSY

It is difficult to predict individual patient responses to AEDs. One of two patients with clinically similar seizures, as well as EEG and imaging findings, may become seizure free forever on a low dose of carbamazepine, for example, whereas the other may remain refractory to maximally tolerated doses of all available AEDs. In addition, some patients may have a good response initially, only to experience a loss of drug effect and development of “intractable” epilepsy. The cause of drug resistance is unknown. In recent years, two hypotheses have been advanced which have received substantial support, at least in preclinical models: the multidrug transporter hypothesis and the drug target hypothesis [149, 150, 150a]. The multidrug transporter hypothesis posits that multidrug efflux transporters overexpressed in epileptic brain regions limit access of AEDs to target sites. In the brain, multidrug transporters, including P-glycoprotein (P-gp), multidrug resistance proteins (MRPs), and breast cancer resistance proteins (BCRPs), are located in the apical (luminal) membrane of endothelial cells that form the blood–brain barrier. These transporters serve to extrude many lipophilic drugs, thus reducing their brain penetration. Several marketed AEDs have been proposed as substrates for P-gp or MRPs, so that overexpression of such transporters at the blood–brain barrier could decrease brain concentrations of these drugs. However, the evidence that all relevant AEDs are substrates is limited [151]; indeed, levetiracetam does not appear to be a substrate [152]. Nevertheless, there is substantial evidence from animal and human studies to support the transporter hypothesis. In particular, numerous studies have shown that
P-gp and other multidrug-resistant proteins are overexpressed in endothelial cells of brain capillaries, and in some instances also in astrocytes and in neurons, in brain tissue resected at epilepsy surgery from patients with drug-refractory epilepsy. In one study, a genetic polymorphism in P-gp, which may enhance transporter activity, was associated with an increased likelihood for pharmacoresistant epilepsy [153, 153a]. However, this association has not been confirmed [154, 155]. The ultimate proof of the transporter hypothesis will require the demonstration that transporter blockers can reverse pharmacoresistance. There are preliminary reports suggesting that this may be feasible, but controlled studies are required [156]. Since multiple different transporters may transport any given drug, highly specific agents may not be effective in all instances.

The drug target hypothesis posits that intrinsic or acquired loss of brain target sensitivity causes AED pharmacoresistance. The target hypothesis is principally based on studies with AEDs on voltage-gated sodium channels. The first in a series of studies examining the hypothesis found that the modulation of sodium current inactivation by carbamazepine in hippocampal CA1 neurons from patients with temporal lobe epilepsy and mesial temporal lobe sclerosis was reduced compared with that in neocortical neurons from the same patients and in CA1 neurons from patients without mesial temporal lobe sclerosis [157, 157a]. In a subsequent study, dentate gyrus granule cell sodium currents in patients with carbamazepine-resistant temporal lobe epilepsy failed to show use-dependent block by carbamazepine [158]. In addition, the fast recovery from inactivation was carbamazepine insensitive. These various results were consistent with the idea that a loss of drug target sensitivity explains the development of drug-resistant epilepsy. A similar loss of sodium channel sensitivity to carbamazepine and phenytoin and in some cases valproate has been found to occur in chronic rat models of epilepsy [157–159]. Alterations of the subunit composition of sodium channels may be present in epileptic animals, but whether this accounts for the pharmacoresistance phenomenon has as-yet not been demonstrated [160].

Little support has been obtained for other proposed mechanisms of pharmacoresistance. For example, a GABA receptor polymorphism associated with intractable temporal lobe epilepsy in an Italian population has not been replicated in France [161, 162]. Moreover, human pathological and imaging studies, including receptor PET and magnetic resonance spectroscopy, have not shown clear differences between drug-refractory and drug-responsive patients.

### 14.12 ALTERNATIVE THERAPIES

#### 14.12.1 Surgery

Temporal lobectomy for the treatment of temporal lobe epilepsy is the most successful operation. In a randomized study, 58% of surgically treated compared with 8% of medically treated patients were free of disabling seizures at one year [6]. Surgical complications occur in about 1% of patients, and death is extremely rare. Extratemporal resections are less successful; 40–50% of patients may become seizure free [163]. Surgical evaluation includes ictal video-EEG monitoring, a variety of imaging studies, and sometimes intracortical electrode studies, in an attempt to localize epileptic foci. Outcome is closely related to the ease of finding a clearly delineated epileptic focus.
14.12.2 Electrical Stimulation

A variety of electrical stimulation techniques have been proposed for the treatment of epilepsy. Only one, vagal nerve stimulation (VNS), is approved by the Food and Drug Administration (FDA) [165]. VNS requires surgical implantation of a stimulation device with a bipolar lead that is attached to the left vagus nerve. The device, which can be programmed externally, delivers a biphasic current that continuously cycles between on and off periods. Typically, 500-μs pulses are delivered at 30 Hz for 30 s “on” time and 5 min “off” time. VNS side effects, which are usually mild, include cough, voice alteration, hoarseness, dyspnea, pain, paresthesia, and headaches. Because patients can sense when VNS is active, controlled trials have compared “high” to “low” stimulation parameters. Efficacy was broadly comparable to new AED trials for refractory CPS, with seizure frequency reductions of 25–30% for high versus 6–15% for low stimulation groups. Open-label extension of the trials indicated that the therapeutic response was sustained [165]. Although VNS is a useful adjunctive therapy for patients with localization-related epilepsy not responding to AEDs or with unacceptable toxicity, very few become seizure free. Moreover, since continuing care is needed, VNS does not offer the sense of “cure” attained by patients who become seizure free after resective surgery and can be withdrawn from all AEDs. VNS has only been shown to be effective for complex partial seizures.

Other electrical stimulation approaches include thalamic and substantia nigra stimulation and direct cortical stimulation via implanted devices. Only limited data have been published [164], and any patient considering these approaches should enroll in a formal clinical trial. Transcranial magnetic stimulation provides an alternative means for the activation of cortical circuits that does not require implantation of a stimulation device.

14.12.3 Diet

The high-fat ketogenic diet has been used for about 75 years for the treatment of intractable epilepsy [166]. The mechanism of the diet is unknown but could relate in part to calorie restriction, which seems to be protective by itself [167], and also to increased levels of acetone, which has anticonvulsant properties [168]. Because the diet is unpleasant, restrictive, and easily evaded, it is usually used for young children with severe secondary generalized epilepsies such as the Lennox–Gastaut syndrome. Unfortunately, controlled studies of the diet have never been published, although many physicians treating patients with epilepsy provide anecdotal evidence of efficacy. Although there is general agreement that the diet reduces seizure frequency, there is little information on potential beneficial or adverse long-term effects of the diet on the course of the underlying seizure disorder.

14.13 TREATMENT OF ACUTE SEIZURES AND STATUS EPILEPTICUS

Most seizures, including GTCSs, stop in under 2 min; subsequent postictal confusion may last about 10 min or less [169, 170]. The most important intervention is to prevent physical injury and assure airway patency. Nothing should ever be placed in the mouth of a person during a seizure, as this can lead to severe injury to teeth.
During the postictal period, patients should be gently restrained from wandering or placing themselves in danger.

Status epilepticus has been defined as two or more sequential seizures without full recovery of consciousness between seizures or more than 30 min of continuous seizure activity. However, increasing recognition of the adverse consequences of prolonged seizures has led to a consensus that intervention should begin after 5 min [171]. Generalized tonic–clonic status epilepticus is a medical emergency that requires aggressive treatment, usually first with a benzodiazepine followed by fosphenytoin (a prodrug for phenytoin) or phenytoin, barbiturates, and, in rare occasions, inhalation anesthetics [171, 172]. Intravenous valproic acid is considered first-line treatment for absence status epilepticus and may be a rational choice in myoclonic status epilepticus and in intractable infantile spasms [173]. While barbiturates and inhalational anesthetic agents have traditionally been used to terminate refractory status epilepticus, recent reports suggest that propofol may also be effective and safe [174]. It is important to remember that patients can have brain injury from prolonged seizures even when paralyzed on a respirator in an intensive care unit; EEG monitoring may be needed. The likelihood of persistent impairment following status epilepticus is strongly related to the underlying etiology and also to the duration; the latter can be affected by treatment. Patients may experience hyperthermia, hypoxia, hypotension, and other metabolic derangements that can contribute to a poor outcome.

14.14 REFLECTIONS

The main pharmacological challenge for patients with epilepsy is to provide effective therapy at the lowest possible toxicity. The “new” antiepileptic drugs introduced in the last 10 years or so have provided some improvements, but they have not substantially decreased the proportion of unresponsive patients, particularly those with secondary generalized epilepsy, for whom there are few other options than drug therapy. Moreover, the long-term effectiveness of the new drugs is uncertain. Only 30–50% of patients remain on a new drug after three years [175, 176].

Some investigators have suggested that new approaches to both drug development and clinical testing are needed. The use of a standard battery of animal models for drug screening has been criticized in the belief that the tests used will fail to identify compounds that act in mechanistically new ways. In fact, it is now clear that the “old-fashioned” models often uncover compounds with distinctive profiles of activity in various types of epilepsy and in addition have unexpected efficacy in nonepilepsy conditions, such as neuropathic pain, bipolar disorder, and migraine [177]. Moreover, the animal models provide an opportunity to identify drugs that act in new ways and through new targets, which would not be available if screens against specific molecular targets were used. Nevertheless, there is considerable interest in including models of refractory pharmacoresistant seizures and chronic epilepsy in the panel of tests used in the early identification of anticonvulsant compounds. Perhaps these newer models will identify drugs that are effective in the treatment of patients that fail to respond to currently available drugs.

The greatest roadblock to the development of new AEDs occurs at the stage of clinical testing. The expense and difficulty of recruiting subjects may be particularly
disadvantageous for “niche” compounds that might be effective for an uncommon epilepsy syndrome or a subset of patients. Commercial sponsors have little incentive to conduct trials in these populations. As a consequence, for many of the newer AEDs, studies have not yet been carried out in such niche populations and we do not know whether they might offer special benefits.

Improved treatment of patients with “refractory” epilepsy in the developed world depends on new basic and clinical research. In contrast, for the majority of people with epilepsy in the world who live in low-income countries and receive no treatment at all [178], a great deal can be done with low-cost treatments such as phenobarbital that could potentially lead to seizure freedom in two-thirds of these individuals [179]. Even in the developed world many patients are not receiving the best current care.

A recent National Institutes of Health conference proposed a paradigm shift in our approach to epilepsy, from symptom control to prevention and cure, defined operationally as “no seizures, no side effects” [180]. Cure is a powerful but elusive concept that is as difficult, perhaps, to measure as to achieve. Our understanding of both the basic mechanisms of epilepsy and its clinical course remains limited; seizures may be only one, though dramatic, symptom of a complex and multifaceted illness. Although curing any form of epilepsy will be exceedingly challenging, the accelerating pace of discovery in basic epilepsy research provides the hope that the tools may one day become available to make this goal approachable. It is sobering, though, to realize how few illnesses, apart from acute infectious diseases, can in fact be cured.

REFERENCES


