Abstract

Epilepsy is a common neurological condition that affects approximately 1% of the general population. In addition, about 10% of the population experiences a seizure sometime during life. The treatment options for epilepsy have come a long way from the bromides to the current era in which we now have multiple treatment modalities, including medications, implantable devices, and surgery. Antiepileptic drugs (AEDs) are the mainstay for treatment of epilepsy with about 70% of children achieving good control with medications alone. The past decade has witnessed the emergence of multiple AEDs—with more than 24 AEDs to choose from presently. The newer drugs provide us with novel mechanisms of action and improved safety profile. This expanded choice of AEDs has made it possible to offer tailored-treatment plans based on unique patient profiles. However, such an ever-increasing choice of medications also poses a challenge for the treating physician as far as choosing the initial drug is concerned—especially because there is limited data comparing the efficacy of one drug to the other. An additional humbling fact remains that, despite an increase in the choice of medications, we are still only able to treat the symptoms of seizures without making any significant progress in reversing or stopping the underlying mechanism of epileptogenesis or in offering neuroprotection from epileptogenesis. Therefore, it is not surprising that, despite the wide array of AED choices, the prevalence of drug-resistant epilepsy has not improved. This article aims at giving a short overview of currently available AEDs. [Pediatr Ann. 2015;44(2):e36-e42.]
Treatment for epilepsy has evolved over the millennia along with our understanding of the disease itself. Seizures have been described as far back as in the Babylonian tablets dating to 1067 BC. Over centuries, seizures were mostly considered to be a form of demonic possession or an act of God and were treated according to the prevailing practices in those communities, including reciting prayers to relieve the evil spirit-causing seizures, and offering gifts to Gods or by wearing amulets. The modern treatment of epilepsy began with potassium bromide, which was first mentioned in the Lancet in 1857.1

SEIZURE MODELS AND THE DEVELOPMENT OF ANTIEPILEPTIC DRUGS

Since the introduction of phenytoin in 1938, the therapeutic potential of antiepileptic drugs (AEDs) has relied heavily on their profiles in animal models of seizures and epilepsy. A new era of systematic AED development began in 1974 when the National Institute of Neurological Disorders facilitated the development of novel chemical entities for the treatment of epilepsy.2 Since then, more than 28,000 investigational chemical entities from academic and pharmaceutical chemists worldwide have been screened.

The Maximum Electroshock Seizure (MES) model, where an electrical stimulus applied through corneal electrodes produces a hind leg tonic extension, is an important first screen for potential drugs that block human tonic-clonic seizures. Models in which chemically induced convulsions are produced by subcutaneous pentylentetrazol are also used for early detection of anticonvulsants.3,4 Investigational AEDs are also assessed in specific animal models such as amygdala or hippocampal-kindled models. More recently, phenotypes consistent with pharmacoresistant epilepsy such as phenytoin-resistant kindled rat have been developed.3

Further, genetic mouse models with features of human epilepsy resulting from a specific gene defect, such as SCN1A, have been developed and are currently being used to study the pathophysiology of epilepsy at the molecular and genetic level. At the present time, these models are not being widely used for drug discovery but in the future may help find a new class of drugs specific for a type of epilepsy. The complete mechanisms of action of several AEDs, including those in common use, have not been fully understood but they can be broadly summarized (Table 1).

CHOOSING THE FIRST ANTIEPILEPTIC DRUG

Fortunately, only about one-third of children who have had a first time seizure will go on to develop epilepsy. The risk of seizure recurrence after a second seizure is much higher (more than 70%); therefore, it is recommended that an AED be initiated after two unprovoked seizures.6 Initiation of therapy after a single unprovoked seizure is controversial. A meta-analyses involving six randomized-controlled trials showed that treatment with an AED after a single seizure reduced the risk of a subsequent seizure in the short-term, but did not alter long-term outcomes.7 The American Academy of Neurology guidelines state that the “treatment with AED is not indicated for the prevention or development of epilepsy and treatment with AED may be considered in circumstances where benefits of reducing a second seizure outweigh the risk of side effects.”

With more than 24 AEDs to choose from, we can now customize therapy for individual patients; yet, we also face the difficult task of choosing the correct first drug. Often, the first drug choice is based on the patient’s unique characteristics. Trials have shown that 47% of patients became seizure free on the first appropriately

<table>
<thead>
<tr>
<th>Mechanisms of Action of Several Antiepileptic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulation of ion channels</td>
</tr>
<tr>
<td>The excitability of neurons is controlled by voltage-gated ion channels that regulate flow of cations. Sodium channels are primary targets of many AEDs such as phenytoin, carbamazepine, and lacosamide. Examples of drugs that act on calcium channels are lamotrigine and ethosuximide. The only AED that modulates potassium channel is ezogabine.</td>
</tr>
<tr>
<td>Enhancement of inhibitory neurotransmission</td>
</tr>
<tr>
<td>GABA is the predominant inhibitory neurotransmitter in the central nervous system. Several AEDs act on different phases of the GABA cycle. Phenobarbital and benzodiazepines bind to distinct sites on GABA-A receptor complex while felbamate and topiramate also activate the GABA-A receptor. Vigabatrin acts by irreversibly inhibiting the enzyme GABA-transaminase and tiagabine by preventing reuptake of GABA from the synaptic cleft.</td>
</tr>
<tr>
<td>Attenuation of excitatory neurotransmission</td>
</tr>
<tr>
<td>Glutamate is the primary excitatory neurotransmitter. None of the current AEDs, except perampanel, have their sole mechanism of action on glutamate. Felbamate and topiramate exert their antiepileptic action through multiple mechanisms—attenuation of excitatory neurotransmission is one of them.</td>
</tr>
<tr>
<td>Novel mechanism</td>
</tr>
<tr>
<td>The newer AEDs tend to have novel mechanisms. Levetiracetam and brivaracetam bind to the SV2A protein on presynaptic vesicles. Various theories have been proposed regarding the function of SV2A, including trapping neurotransmitter molecules, modification of synaptic vesicle exocytosis, and regulating vesicle shape and trafficking. However, these mechanisms have not been confirmed.</td>
</tr>
</tbody>
</table>

Abbreviations: AEDs, antiepileptic drugs; GABA, gamma-aminobutyric acid.
selected and dosed AED. The International League Against Epilepsy (ILAE) recently made available the evidence for choosing initial monotherapy. The findings for different categories of seizures are: (1) Children with partial onset seizures: oxcarbazepine has level A evidence; carbamazepine, phenytoin, phenobarbital (PB), topiramate, valproic acid, and vigabatrin have level C evidence; and clobazam, lamotrigine (LTG), and zonisamide have level C evidence; (2) Children with generalized tonic-clonic seizures: inadequate data exist for evidence-based recommendations; carbamazepine, phenobarbital, phenytoin, topiramate, and valproic acid have level C evidence; (3) Children with absence epilepsy: ethosuximide and valproic acid have level A evidence.

These results were provided to show available evidence but for an individual patient, the ILAE recommends that the treating physician use their judgment in selecting the appropriate initial AED.

**Monotherapy Versus Polytherapy**

Although it is ideal to achieve seizure freedom with monotherapy, less than 50% of patients are able to achieve that with the first drug. When switching AEDs, it is advisable to switch gradually, giving enough time for the new drug to achieve therapeutic levels before starting the withdrawal of the original drug. The patient is thus protected from having a breakthrough seizure from having subtherapeutic levels of either drug. With this approach, about 14% of patients who are resistant to the initial therapy achieve seizure freedom with alternative monotherapy.

Patients who do not achieve seizure freedom after adequate trials of at least two appropriate AEDs given as monotherapy or in combination are considered to be pharmacoresistant or to have refractory epilepsy, per the 2010 ILAE definition. In these patients chances of achieving seizure freedom with additional AED trials are very low; hence, nonpharmacological treatments like epilepsy surgery should be concurrently considered.

For patients in whom polytherapy has to be used, certain principles that allow for safe and optimal combination therapy should be followed: (1) Do not prescribe drugs in the same class in order to avoid cross sensitivity if there were allergic reactions to one drug, ie, carbamazepine and oxcarbazepine; (2) When possible, use combinations that have synergistic effects (valproic acid [VPA] and LTG); (3) Combine drugs with different mechanisms of actions; (4) Anticipate and adjust drug doses appropriately when using drugs that influence serum levels of other drugs (ie, VPA increases serum LTG level, and therefore a lower dose of LTG is needed and is better tolerated).

**FIRST-GENERATION ANTIEPILEPTIC DRUGS**

**Phenobarbital**

PB is one of the earliest AEDs. It was first introduced as a sedative and in 1912 was accidently discovered to have antiepileptic effect. It is still widely used in developing countries. It is effective against most types of seizures except absence. Since it was released into the market prior to 1934, PB has not undergone rigorous trials, per the current US Food and Drug Administration (FDA) regulations, but has been compared with established AEDs including phenytoin and carbamazepine. When compared to phenytoin, no difference was found in primary outcomes but PB was more likely to be discontinued due to side effects of irritability and hyperactivity. It is available in both intravenous (IV) and oral formulations. It still plays a major role in the treatment of neonatal seizures and especially in the treatment of status epilepticus. Caution is advised when discontinuing phenobarbital, because rapid withdrawal may cause withdrawal seizures.

**Phenytoin**

Since its introduction in 1938, phenytoin (PHT) remains one of the most widely used AEDs. It is used in the treatment of partial and generalized seizures and remains one of the few drugs studied for effectiveness in status epilepticus.

PHT is highly protein bound (>90%) to albumin. In relative hypoalbumin states, the total level of phenytoin may be misleading as the percentage of the free (nonprotein bound) component of the drug will be higher. PHT also has nonlinear kinetics. As the dose and concentration of the drug increase, the eliminating mechanisms become saturated. This causes disproportional increase in PHT serum level with small increments to the dose at higher levels. PHT also has interactions with other tightly protein bound drugs like VPA and can increase their active drug levels.

PHT is available as an IV formulation. However, this has been largely replaced by the use of IV fosphenytoin. Rapid infusion of IV PHT can cause hypotension and cardiac arrhythmias and its extravasation in subcutaneous tissue results in a serious local reaction called purple glove syndrome. IV fosphenytoin does not carry these risks, and is the preferred formulation when parenteral phenytoin use is indicated.

PHT is not as sedating as the drugs that were available prior to it, but has some significant side effects especially when used over long durations including gingival hypertrophy, coarse facial features, hirsutism, and osteoporosis. High serum levels cause nystagmus, ataxia, drowsiness, and incoordination.

**Valproic Acid**

VPA is approved for almost all types of seizures and is one of the widely used AEDs not only for epilepsy but also as a mood-stabilizing drug. Valproate is available in many formulations including extended release, sprinkles, liquid, and IV. It is very well absorbed orally, and is 90% protein bound. VPA inhibits the cytochrome P450 system and raises the levels of AEDs metabolized through this system. It also displaces other highly protein-bound drugs such as PHT and can raise their free
fraction. When used with LTG, it can raise LTG levels and precipitate fatal skin reactions such as Stevens-Johnson syndrome.

Side effects include weight gain (up to 30% of users), dose-related tremor, alopecia, hirsutism, and menstrual cycle irregularities in women. It can cause an idiosyncratic fatal hepatic necrosis and elevated ammonia levels. It has the highest incidence of fetal malformations among all AEDs when used during pregnancy and should be used with caution in teenage girls.

**Ethosuximide**

Ethosuximide (ETX) has been available since 1958 and is currently indicated only for treating typical childhood absence epilepsy.  

**Carbamazepine**

Carbamazepine (CBZ) has been available in the United States since 1974 and is FDA approved for the treatment of partial and generalized seizures but it may aggravate certain generalized epilepsies like absence epilepsy.

CBZ has about an 80% absorption rate and is about 75%-85% protein bound. An important aspect of CBZ is that it induces its own metabolism by stimulating cytochrome P450 and, hence, needs dose adjustment as serum levels fall after the first few weeks of treatment and should not be mistaken for noncompliance. CBZ has multiple interactions as an enzyme inducer and affects drugs that are metabolized in the liver.

CBZ can cause diplopia, weight gain, rash, hyponatremia, leukopenia, hepatotoxicity (rarely), and other idiosyncratic reactions. When prescribing for patients of Southeastern-Asian origin, it should be kept in mind that there is a strong association with HLA-B*15.02 and severe cutaneous adverse effects such as toxic epidermal necrolysis or Stevens-Johnson syndrome and it carries a black box warning for the same.

It is available in both oral, extended release, and IV formulations, and can be rapidly titrated to target dose.

Somnolence was the most common reason for discontinuation in the US pivotal trial (5% to 20%) but behavioral/psychiatric adverse effects were more prominent in subsequent trials (13.5% for patients on levetiracetam versus 6% for placebo-treated patients).

**Lamotrigine**

LTG has been available in the United States since 1994 and has been FDA approved for use in partial and generalized convulsive seizures. LTG is considered a broad-spectrum AED. When a patient

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**TABLE 2.** First-Generation Antiepileptic Drugs, Recommended Dosage, and Laboratory Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose/Day</th>
<th>Maintenance Dose/Day</th>
<th>Dosing Schedule</th>
<th>Half-life (hours)</th>
<th>Laboratory/Clinical Monitoring</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHB</td>
<td>3 mg/kg</td>
<td>3-6 mg/kg</td>
<td>QD-BID</td>
<td>24-140</td>
<td>Sedation, CBC, LFT, serum levels</td>
<td>Suspension, pills, IV</td>
</tr>
<tr>
<td>PHT</td>
<td>4 mg/kg</td>
<td>4-8 mg/kg</td>
<td>QD-TID</td>
<td>7-42</td>
<td>CBC, LFT, serum levels</td>
<td>Suspension, capsule, IV</td>
</tr>
<tr>
<td>VPA</td>
<td>15 mg/kg</td>
<td>15-45 mg/kg</td>
<td>TID-QID</td>
<td>5-15</td>
<td>CBC, LFT</td>
<td>Sprinkle caps, tablets, suspension, IV</td>
</tr>
<tr>
<td>CBZ</td>
<td>10 mg/kg</td>
<td>10-35 mg/kg</td>
<td>TID</td>
<td>25-65</td>
<td>CBC, LFT</td>
<td>Suspension, capsule</td>
</tr>
<tr>
<td>ETX</td>
<td>15 mg/kg</td>
<td>15-40 mg/kg</td>
<td>QD-BID</td>
<td>30-40</td>
<td>CBC, LFT</td>
<td>Liquid, capsule</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice a day; CBC, complete blood count; CBZ, carbamazepine; ETX, ethosuximide; IV, intravenously; LFT, liver function test; PHB, phenobarbital; PHT, phenytoin; QD, once a day; TID, three times a day; VPA, valproic acid.
When patients have multiple seizure types or when the type of seizures a patient is having is not clear, choosing a broad-spectrum antiepileptic drug is preferable (Table 4).

It is well absorbed and has 100% bioavailability. Enzyme-inducing drugs like phenytoin and carbamazepine reduce LTG levels, whereas valproate increases LTG serum levels by enzyme inhibition.

LTG can have serious side effects, including the risk of life-threatening rash (carries a black box warning) in the acute phase and hence has to be titrated very slowly over weeks to achieve the target maintenance dose, which is usually between 200 to 400 mg/day. The rash has been reported in 10% to 12% of patients. It typically appears in the first 4 weeks of therapy and is rarely seen after 8 weeks. LTG is thought of as a good AED due to its favorable long-term side effect profile.

**Oxcarbazepine**

Oxcarbazepine (OXC) was FDA-approved in 2000 as a monotherapy or adjunct treatment for partial seizures and has now become one of the most commonly used drug for partial onset seizures in children. OXC is rapidly converted into 10-mono-hydroxy derivative that is responsible for most of the antiepileptic effect. OXC has little to no effect on most AEDs. Although OXC and CBZ share a common mechanism of action, some patients who are inadequately treated with CBZ improve after switching to OXC.

Side effects with OXC include hyponatremia (more frequently than CBZ) and allergic rash. In general, it is much more tolerable than CBZ. Allergic cross-reac-

### Table 3. Second-Generation Antiepileptic Drugs, Recommended Dosage, and Laboratory Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose/Day</th>
<th>Maintenance Dose/Day</th>
<th>Dosing Schedule</th>
<th>Half-life (hours)</th>
<th>Laboratory/Clinical Monitoring</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBM</td>
<td>15 mg/kg</td>
<td>15-45 mg/kg</td>
<td>TID</td>
<td>20-30</td>
<td>CBC, LFT</td>
<td>Suspension, pills</td>
</tr>
<tr>
<td>GBP</td>
<td>10 mg/kg</td>
<td>25-50 mg/kg</td>
<td>TID</td>
<td>4-7</td>
<td>Weight</td>
<td>Suspension, caps, IV</td>
</tr>
<tr>
<td>LTG</td>
<td>0.15-0.5 mg/kg</td>
<td>5-15 mg/kg (very slow titration)</td>
<td>BID</td>
<td>6-11</td>
<td>Rash, CBC, LFT</td>
<td>Pills (chewable and dispersible)</td>
</tr>
<tr>
<td>LEV</td>
<td>10 mg/kg</td>
<td>40-100 mg/kg</td>
<td>BID</td>
<td>6-8</td>
<td>Behavior</td>
<td>Pills, liquid, IV</td>
</tr>
<tr>
<td>OXC</td>
<td>8-10 mg/kg</td>
<td>30-46 mg/kg</td>
<td>BID</td>
<td>7-9</td>
<td>BMP, hyponatremia</td>
<td>Pills, suspension</td>
</tr>
<tr>
<td>TPM</td>
<td>1-3 mg/kg</td>
<td>5-9 mg/kg</td>
<td>BID</td>
<td>8-12</td>
<td>Weight, renal stones, cognition, ocular pressure</td>
<td>Pills, sprinkle capsules</td>
</tr>
<tr>
<td>ZNS</td>
<td>2-4 mg/kg</td>
<td>4-12 mg/kg</td>
<td>BID</td>
<td>63</td>
<td>None</td>
<td>Capsules</td>
</tr>
</tbody>
</table>

*Abbreviations: BID, twice a day; BMP, basic metabolic profile; CBC, complete blood count; FBM, felbamate; GBP, gabapentin; IV, intravenous; LEV, levetiracetam; LFT, liver function test; LTG, lamotrigine; OXC, oxcarbazepine; TID, three times a day; TPM, topiramate; ZNS, zonisamide.

### Table 4. Classification of Antiepileptic Medications as Broad or Narrow Spectrum

<table>
<thead>
<tr>
<th>Broad Spectrum</th>
<th>Narrow Spectrum</th>
<th>Seizure Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Carbamazepine</td>
<td>Absence</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Ezogabine</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Gabapentin</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Oxcarbazepine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Perampanel</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Phenytoin</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Pregabalin</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Valproate</td>
<td>Tiagabine</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Vigabatrin</td>
<td></td>
</tr>
</tbody>
</table>

*Available as intravenous formulation.
CME

Activity with CBZ occurs in about 25% of patients.\(^{17}\)

**Topiramate**

Topiramate (TPM) is a broad-spectrum AED that was approved by the FDA in 1997 for adjunctive treatment of partial seizure and has received additional indications for primary generalized tonic-clonic seizures.\(^{18}\)

TPM is well absorbed orally, is minimally protein bound, and has few if any drug interactions. Major side effects to consider are cognitive impairment, renal stones, speech problems, and weight loss.

**THIRD-GENERATION ANTIEPILEPTIC DRUGS**

Please see Table 5 for a full description of drugs in this class. Most of the drugs in this class are used as add-on drugs after medications from the first and second generation have failed. As such, they are primarily used by child neurologists and therefore only a brief overview of vigabatrin will be provided as it is often used in the treatment of infantile spasms.

**Vigabatrin**

Vigabatrin (VGB) has serious side effects, but was finally approved by the FDA in 2010 after being approved internationally for some time. It has been approved for infantile spasms especially with tuberous sclerosis and refractory partial epilepsy. VGB has good oral bioavailability and is excreted unchanged by the kidney and has minimal interactions with other AEDs.

VGB causes irreversible bilateral concentric visual field constriction in 30% or more patients. It is unpredictable and can happen at any time during treatment. Because of these serious side effects, use of VGB is limited and families are advised to stop treatment if there is no significant improvement of seizure symptoms after 3 months of therapy.\(^{19}\)

**Clobazam**

Clobazam was an orphan drug, which was approved by the FDA in 2011 for use as an adjunctive treatment in patients with Lennox-Gastaut syndrome. It is a benzodiazepine and acts by potentiation of GABAergic neurotransmission by binding to the GABA-A receptor.

Sedation is the main side effect but is not as severe as seen with other benzodiazepines. Caution is warranted when withdrawing, because withdrawal symptoms/seizures can occur.

**ANTIEPILEPTIC DRUGS IN PREGNANT WOMEN**

AEDs pose unique challenges in women, especially in those of childbearing age and during pregnancy. Careful consideration of maternal and fetal health is warranted when using AEDs.

The risk for congenital malformations is higher in infants born to women taking AEDs during pregnancy when compared to those born to women not on AEDs. The most common malformations include cleft lip or palate, neural tube defects, and congenital heart disease.

All available AEDs between 1997 and 2011 were analyzed in the North American registry. Rates for major congenital malformations in women on monotherapy in the first trimester ranged from 9.3% for VPA to 2% for LTG.\(^{20}\) There is also evidence that fetal exposure to VPA has dose-dependent associations with reduced cognitive abilities across a range of domains when compared at age 6 years.\(^{21}\)

Based on the data from the various pregnancy registries, it is advised to use monotherapy with the lowest possible dose and to avoid VPA if possible.

**DRUGS THAT WORSEN SEIZURES**

Certain medications, including AEDs, can worsen seizures. Drugs such as bupropion, tramadol, clozapine, and olanzapine can lower the seizure threshold in patients with epilepsy. AEDs such as carbamazepine when given in patients with absence epilepsy or in patients

### TABLE 5.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose/Day</th>
<th>Maintenance Dose/Day</th>
<th>Dosing Schedule</th>
<th>Half-life (hours)</th>
<th>Laboratory/ Clinical Monitoring</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLB</td>
<td>5 mg</td>
<td>20-40 mg</td>
<td>BID</td>
<td>36-42</td>
<td>None</td>
<td>Suspension, pills</td>
</tr>
<tr>
<td>LCM</td>
<td>1 mg/kg</td>
<td>2-8 mg/kg(^a)</td>
<td>BID</td>
<td>13</td>
<td>None</td>
<td>Pills oral, solution, IV</td>
</tr>
<tr>
<td>PER</td>
<td>2 mg</td>
<td>8-12 mg</td>
<td>QHS</td>
<td>105</td>
<td>None</td>
<td>Pills</td>
</tr>
<tr>
<td>RUF</td>
<td>10 mg/kg</td>
<td>45 mg/kg</td>
<td>BID</td>
<td>6-10</td>
<td>EKG (QT interval)</td>
<td>Suspension, pills</td>
</tr>
<tr>
<td>VGB(^b)</td>
<td>50 mg/kg</td>
<td>50-150 mg/kg</td>
<td>BID</td>
<td>5-9</td>
<td>Visual fields</td>
<td>Powder, pills</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice a day; CLB, clobazam; EKG, electrocardiogram; IV, intravenous; LCM, lacosamide; PER, perampenel; RUF, rufinamide; VGB, vigabatrin; QHS, every day at bedtime.

\(^a\)Maximum dose: 400 mg.

\(^b\)For infantile spasms.
with generalized epilepsy can exacerbate seizures. When AEDs such as phenytoin reach toxic levels, they can cause paradoxical increase in seizures. Other situations when drugs can worsen seizures are when AEDs are rapidly withdrawn—especially benzodiazepines and phenobarbital. This observation is based on retrospective data and needs more evaluation.

**DISCONTINUATION OF ANTIEPILEPTIC DRUGS**

Once patients are seizure free for a few years, the question always comes up if AEDs should be continued, reduced, or stopped. The evidence to guide AED discontinuation is insufficient and, hence, the decision to withdraw medications should be individualized and thoroughly discussed. The 1996 American Academy of Neurology practice parameters suggest that when an individual is seizure free for 2-5 years on AEDs, has a single type of seizure, has a normal physical examination, and a normalized electroencephalogram (EEG) with antiepileptic medications on board, an attempt can be made to gradually wean off AEDs. A more recent 2004 review of 28 studies showed that predictors of higher risk of recurrence included adolescent-onset epilepsy syndromes (like juvenile myoclonic epilepsy), focal seizures, underlying neurological disorder, and children with abnormal EEG at the time of withdrawal.

**CONCLUSIONS**

With the ever-increasing armamentarium of available AEDs, many—but not all—patients achieve good control of seizures. It is also possible now to control seizures with fewer side effects, drug interactions, and need for laboratory monitoring. However, there will still be a group of refractory epilepsy patients in whom achieving complete seizure control will not be possible with medications alone. The goal for these patients should be pursuing other modalities of treatment (surgery, devices, or diet) at the earliest and if everything else fails, the goal should be in achieving a better quality of life by simplifying the number of medications or doses to minimize side effects.

With all AEDs there are still risks that are inherent to the group as a whole and should be discussed. Calcium and vitamin supplementation should be provided to minimize the risk of bone loss/fracture with the long-term use of AEDs. All AEDs carry a somewhat high risk of causing congenital malformations and when started on a new AED, there seems to be an increase in the risk for suicide initially and patients and families should be counseled. Whenever possible patients should be on a minimal number of AEDs with the lowest effective dose, and withdrawal of an AED should be considered when seizure freedom of 2-3 years has been achieved.

**REFERENCES**