Childhood epilepsy differs from epilepsy in adulthood because of age-related seizure types, etiologies of seizures, the presence of both benign and malignant epilepsy syndromes, and the frequent presence of concomitant neurologic abnormalities, mental retardation, or behavioral difficulties in those with refractory seizures. Children may also respond differently to antiepileptic drugs (AEDs) during treatment; what seems to be a natural first-choice drug for an adult with a particular seizure type may be more or less preferred at different stages of childhood. Defining the presumptive syndrome of epilepsy for each patient, even upon presentation with a possible first seizure, allows one to tailor initial treatment and choose the most appropriate drug.

One must carefully differentiate between seizures seen in the neonate, child, or adolescent, as the same seizure type may represent completely different epilepsy syndromes and may require different types of therapy depending on the patient’s age. In addition, for those with lesional epilepsy who are possible candidates for surgery, brain plasticity offers a special opportunity for early surgical intervention. These children may need only brief drug treatment after more definitive therapy.

Perhaps most importantly, a single seizure may not need therapy at all, especially if it was unprovoked. A decision to treat usually depends on whether seizure activity recurs or whether multiple risk factors for recurrence are present. Efficacy is the first consideration, but AED selection may be equally dependent upon concomitant diagnoses, expected length of therapy, and perception of side effects.

**Diagnostic Considerations**

Most seizures should be treated acutely if the child is actively seizing when presenting to the physician. Most acute treatment centers offer the use of benzodiazepines, phenobarbital, phenytoin (PHT) (fosphenytoin), and, most recently, intravenous valproate. Treating with loading doses of medication after the event has ceased only clouds the examination and one’s initial diagnostic evaluation. The finding of hypoglycemia or electrolyte imbalance removes the need for drug treatment. If seizures recur after the first event, they should be carefully investigated before chronic therapy is initiated.

A description of the event is crucial, especially in young children. In neonates and infants, contradictory information may arise from the electroencephalogram (EEG) and clinical description. Seizures, furthermore, may change their clinical appearance (semiology) as they recur in the same child or as the child matures. So determining the exact seizure type in some children may actually be difficult. Furthermore, in some children with generalized encephalopathic processes, partial seizures may be the first presentation, only to be complicated later by generalized seizures such as infantile spasms, atypical absences, and atonic or myoclonic events.

Electroclinical correlation is extremely important before embarking on a choice of the initial AED. Diagnostic studies may also distinguish seizures resulting from benign syndromes from those that are symptomatic and typically more difficult to control.

**Choice of Drug**

The AED of choice should completely control seizures without producing adverse effects. The optimal drug for all children with all seizure types is still not known. The physician, then, must make a decision to treat with a given drug...
that is likely to control symptoms in the individual child while producing the least amount of toxicity. In children with concomitant diseases, behavioral disorders, or other symptoms, one must select drugs that would be least likely to exacerbate side effects.

Children who are hyperactive should not initially be given agents that will make them more irritable, less attentive, and more of a behavioral problem. Those with motor disturbances should not be given medications likely to aggravate incoordination. Those already exhibiting tremor disturbances should not receive medications that will make them more irritable, less attentive, and more of a behavioral problem. Children who have eating disorders must not receive medications that would exacerbate obesity or anorexia. Because generalized seizures are more common in children, clinicians treating pediatric epilepsy are more likely to use medications such as ethosuximide (ESX), valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), and zonisamide (ZNS) that are broadly effective in partial and generalized seizures. Carbamazepine (CBZ), PHT, gabapentin (GBP), tiagabine (TGB), and oxcarbazepine (OXC), along with the broader-spectrum AEDs listed above and vigabatrin, should be given appropriately for partial seizures and convulsions. The exact role of levetiracetam (LVT) and ZNS is being further explored but may well extend beyond partial seizures. Phenobarbital (PB) was, for many years, the mainstay of therapy for many types of epilepsy. The practice of prescribing phenobarbital should be reconsidered because of its considerable toxicity and the availability of equally effective AEDs with fewer adverse events, especially neurotoxicity. Similarly, the use of benzodiazepines for chronic therapy may produce more behavioral and neurotoxic adverse effects.

In general, monotherapy is desirable. Unfortunately, physicians treating children who have seizures do not always possess up-to-date, comparative data concerning childhood epilepsy and treatment with antiepileptic drugs, especially the new drugs. Clinical studies designed for the licensing of new compounds rarely give sufficient information to determine the ultimate dosing and use characteristics that will be determined after long-term use in much larger populations of patients. In addition, pediatric studies are typically performed well after the initial studies are done in adults with refractory partial seizures.

Almost all drugs shown to be efficacious in adult partial seizures have been of similar utility in children, and none has been shown to be useful as adjunctive therapy and not useful as monotherapy. The most challenging question is when to use the new agents as monotherapy and in children, as the initial data will first favor use as adjunctive therapy in adults. Several drugs, however, have been studied in children with encephalopathic epilepsy, such as Lennox-Gastaut syndrome. Although similarities exist, differences allow some distinction of these agents.

AED Characteristics

This section briefly reviews the properties associated with both classic and newer AEDs. Table 21-1 lists drugs introduced since 1993 for the treatment of epilepsy. Not all have undergone trials in children and therefore, in a strict sense, they are not “indicated for use in childhood epilepsy.” Nevertheless, approval of these agents has demanded that further studies be done to establish their efficacy, safety, and pharmacokinetics when used in children of different ages. Figure 21-1 demonstrates the seizure types for which drugs are useful.

Classic AEDs

CBZ, clonazepam, ESX, PB, PHT, primidone, and VPA have been reviewed extensively for their use in both children and adults.

Carbamazepine

CBZ is the drug of choice for many physicians in treating partial seizures and generalized tonic-clonic seizures. Its mechanism is similar to that of PHT and is through the modulation of neuronal sodium channels. It remains one of the classic drugs in the treatment of both benign and refractory partial seizures with or without secondary generalization. The most common adverse effects involve neurotoxicity. This is frequently dose-related or dependent on too-rapid titration initially. Although doses of 15 to 20 mg/kg/d may be needed in children on monotherapy, usual starting doses are one-third to one-half of this total dose, with increments performed every 1 to 2 weeks. With a relatively short half-life in children (especially when using combination therapy or switching from another enzyme-inducing compound), CBZ should be taken at least three times daily, which usually can be accomplished in school-aged children before and after school and in the evening. With the availability of extended- or continuous-release formulations, twice-daily dosing is acceptable.

In the past, the rare complications of aplastic anemia and organ toxicity were feared, and frequent complete blood counts and liver function tests were recommended. Clinical monitoring seems the most appropriate, with blood testing only at initiation of therapy as one is evaluating the patient for causes of epilepsy and when clinical symptoms suggest the need for further studies. Neurotoxic effects typically include diplopia, ataxia, nausea, vomiting, incoordination, and somnolence. An idiosyncratic rash may develop, and hyponatremia seems to be a rare complication. Overall, the rash rate is approximately 10%, and idiosyncratic serious rash seems to be much less common.
**Ethosuximide**

ESX is indicated for use in children with absence seizures. Its mechanism of action involves reduction of low-threshold T-type calcium currents, with disruption of slow rhythmic firing of thalamic neurons. The efficacy of this agent is against absence seizures, with little effect on other types of epilepsy. For some, this agent remains the first-line antiabsence AED because of its long-established safety and efficacy. It should be titrated gradually to reduce dose-related side effects, which include neurotoxicity and very significant gastric distress. Ultimate doses of 14 to 40 mg/kg/d are usually divided and given with meals to decrease gastric discomfort. Besides abdominal pain, nausea, vomiting, weight loss, and psychological or behavioral disturbance, drowsiness, rash (rare), and lupus-type syndrome have been noted.

**Phenytoin**

PHT is indicated for use against partial seizures with or without secondary generalization. Its mechanism of action is through the sodium channel to stop repetitive neuronal firing and spread of abnormal discharges. Available as a parenteral formulation for years, the PHT prodrug fosphenytoin should replace most parenteral PHT use because of decreased peripheral vascular complications and cardiovascular toxicity resulting from the absence of the diluent used in parenteral PHT. Additionally, fosphenytoin can be loaded, 20 mg/kg, three times faster than PHT when needed acutely. Maintenance doses usually are between 4 and 12 mg/kg/d. Because of its nonlinear kinetics, this drug is more difficult to dose precisely while keeping in the therapeutic range without increased toxicity or subtherapeutic serum levels. In neonates, it has a more prolonged half-life, but shortens by the time a child reaches 3 months of age. The half-life may be as short as 8 to 12 hours in younger children, whereas it nears 24 hours in adolescents and adults. It is an enzyme-inducing AED and will complicate therapy with other agents. Its metabolism may be induced. In addition, it is highly protein-bound. When other drugs with significant protein binding are

---

**FIGURE 21-1. Treatment options.**

<table>
<thead>
<tr>
<th>Partial</th>
<th>Generalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Complex Secondary generalized</td>
<td>Tonic-clonic</td>
</tr>
<tr>
<td>Tonic</td>
<td>Myoclonic</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>Atonic</td>
<td>Steroids</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>TGB?</td>
</tr>
<tr>
<td>Absence</td>
<td>VPA, LTG, TPM, (FBM), ZNS</td>
</tr>
</tbody>
</table>

PHT = phenytoin; CBZ = carbamazepine; PB = phenobarbital; GBP = gabapentin; TGB = tiagabine; LVT = levetiracetam; OXC = oxcarbazepine; TPM = topiramate; FBM = felbamate; VGB = vigabatrin; ESX = ethosuximide; VPA = valproic acid; LTG = lamotrigine; ZNS = zonisamide.
administered, interactions are likely. Its nonlinear pharmacokinetics and cosmetic side effects have made it a less-preferred drug for chronic therapy.

Nevertheless, PHT remains a favorite of general practitioners for the treatment of new-onset epilepsy in adults. Besides neurotoxic dose-dependent CNS effects (including nystagmus, ataxia, dysarthria, and somnolence), gingival hypertrophy (seemingly patient specific) and idiosyncratic effects (including rash, rare hepatic dysfunction, and lymphadenopathy) have been noted. Coarsening of features seems to be more common when PHT is used in combination with barbiturates.

Primingone

Primidone is less frequently used as first-line therapy in children with partial and secondary generalized seizures. In the adult Veterans Administration Cooperative Study, its efficacy was similar to that of PB, PHT, and CBZ, but it was poorly tolerated during initial phases of dosing. It is, therefore, not considered a primary first-line drug for the treatment of childhood epilepsy.

Valproic Acid

Valproic acid was the first of the AEDs with broad-spectrum efficacy introduced to treat not only partial but also generalized seizures of various types, including absence (both typical and atypical), atonic, and myoclonic seizures. It is reported to be effective against infantile spasms as well. Its primary drawback is the potential for producing hepatotoxicity, especially in young children. VPA-associated hepatotoxicity of this type occurs most frequently in the first 90 days of therapy and rarely after the first year of chronic therapy. A potentially idiosyncratic type of liver failure is associated with microvesicular steatosis and may be associated with specific underlying inborn metabolic defects or acquired mitochondrial dysfunction. It is most commonly noted when used in polytherapy with enzyme-inducing AEDs in children under the age of 2 years who have preexisting encephalopathy or metabolic disease. During polytherapy, omega oxidation through cytochrome P-450 is enhanced with the production of a toxic (4-ENE) metabolite. This compound, along with other possible toxic metabolites, may be responsible for mitochondrial failure. When used as monotherapy, even in very young children, the risk of potentially fatal hepatotoxicity is markedly decreased.

More common side effects include neurotoxicity, including somnolence, tremor, and behavior change. Tremor is certainly dose-related. Thrombocytopenia may be seen when doses are significantly elevated. Rarely, pancreatitis has been reported as a probable idiosyncratic effect, most commonly associated with hepatotoxicity.

VPA should be initiated at or below approximately 15 mg/kg/d and increased to 60 mg/kg/d if symptoms have not yet been controlled and depending on tolerability. Higher doses frequently are given to children, especially to those on enzyme-inducing AEDs. The VPA preparation has a relatively short half-life, and gastrointestinal side effects are more common. Administration with food and in divided doses, three or four times daily, allows better tolerability. Enteric-coated preparations are preferred, with a marked reduction of digestive tract symptoms. Sprinkle and extended-release preparations require less-frequent dosing and offer smoother pharmacokinetics.

The association of VPA therapy with weight gain has been long established. Also, an increased incidence of polycystic ovary syndrome is noted in some women, especially those who experience weight gain. Increased incidence of neural tube defects also has been documented in offspring of mothers receiving VPA during the first trimester; folate administration and specific fetal monitoring should be instituted.

Nevertheless, with appropriate clinical monitoring, this drug is the best-accepted long-term therapy for patients with primary generalized and symptomatic generalized epilepsy because of its proven efficacy. The efficacy of VPA and its side effect profile are being compared with those of newer drugs as they are introduced. More data are required before concluding that newer agents are preferable to VPA for first-line therapy.

Newer AEDs

The anticonvulsants listed in Table 21-1 have been approved for use in the United States since 1993. With few exceptions, initial approval was for use as adjunctive therapy in adults with partial seizures. Felbamate (FBM) and OXC were evaluated in monotherapy trials as part of their early testing, which allowed labeling, including their use as monotherapy. Monotherapy trials in children followed the initial treatment protocols in adults. In some cases, withdrawal of adjunctive treatment provided data on monotherapy. This experience, of course, is of extreme importance in establishing the possible utility of these new agents as first-line treatment. Other needed information balances

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Felbamate (Felbatol&lt;sup&gt;(1)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1993</td>
<td>Gabapentin (Neurontin&lt;sup&gt;(2)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1994</td>
<td>Lamotrigine (Lamictal&lt;sup&gt;(3)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1996</td>
<td>Topiramate (Topamax&lt;sup&gt;(4)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1997</td>
<td>Tiagabine (Gabitril&lt;sup&gt;(5)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1999</td>
<td>Levetiracetam (Keppra&lt;sup&gt;(6)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>2000</td>
<td>Oxcarbazepine (Trileptal&lt;sup&gt;(7)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>2000</td>
<td>Zonisamide (Zonegran&lt;sup&gt;(8)&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Pending</td>
<td>Vigabatrin (Sabril&lt;sup&gt;(9)&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>
advantages over existing therapy by examining reported adverse effects, ease of use, and, perhaps most importantly, overall efficacy against partial seizures and other seizure types that may not have been included during initial studies.

A brief review of each new AED is presented below. Special considerations in children, such as possible effects on behavior, cognition, sleep, and growth, and positive or negative effects on comorbid disease states and their treatment ultimately decide the first-choice AED.

Felbamate
FBM was the first of the new AEDs approved for use in partial and generalized seizures in adults and in children for the treatment of seizure types associated with Lennox-Gastaut syndrome. FBM is a lipophilic, watersoluble dicarbamate thought to act as a blocker of glycine at the N-methyl-D-aspartate (NMDA) receptor, decreasing neuronal permeability to calcium. There is also evidence that FBM acts, in part, by blocking voltage-dependent sodium channels, as seen for CBZ and PHT. In a presurgical trial, 64 adults were randomly assigned to receive either FBM rapidly titrated to 3,600 mg/d for 3 days or placebo added to any remaining AEDs after withdrawal. Only 46% of the patients who received FBM had a fourth seizure within 28 days as opposed to 88% of patients taking placebo. In monotherapy studies, low-dose VPA (15 mg/kg/d) was used as a control in adult patients with uncontrolled partial seizures. A seizure frequency reduction of 50% or more was achieved in 29% of patients on FBM and in 11% receiving low-dose VPA. In the Lennox-Gastaut syndrome trials, patients treated with FBM versus placebo had significantly fewer generalized tonic-clonic and atonic seizures, making this drug one of the most efficacious in the treatment of this encephalopathic epilepsy of childhood.

Drug interactions and adverse events are increased with FBM rapid-dose titration. In adults, a dose of 1,200 mg/d is recommended during the first week, with a reduction of concomitant antiepileptic dose by approxim ate one-third. It is recommended that the FBM dose be increased to 2,400 mg during the second week of treatment and that the concomitant AED dose be further decreased over the second and subsequent weeks. In the third week, the FBM dose should be increased to 3,600 mg. In children, doses of 15, 30, and 45 mg/ kg/d were recommended in a titration schedule similar to that of adults. Slower titration schedules and removing one concomitant medication at a time after the initial one-third reduction allows better success for titration. Some children with refractory epilepsy require daily doses of 75 to 90 mg/kg/d, while adults may require doses of 5,000 to 6,000 mg/d.

For most patients, FBM is not a first-choice therapy because of the associated risk of aplastic anemia. The incidence of aplastic anemia linked to FBM administration is estimated to be approximately 1 in 5,000 to 1 in 4,000 treated patients. At highest risk are female patients with prior blood dyscrasia, immune disorders (especially lupus), and prior hypersensitivity to other medications. No child younger than 13 years of age has been reported to have developed FBM-related aplastic anemia, and most cases occurred during the first 6 months of therapy. A toxic metabolite of FBM has been identified, and its concentration or host susceptibility through inadequate glutathione reductase or other scavenger system deficiencies may lead to idiosyncratic reactions. A urine test to assess this metabolic pathway is available. Severe hepatotoxicity also has been associated with FBM administration without a clear predominance in young children, as seen with VPA. The most common adverse reactions associated with FBM administration include anorexia, vomiting, insomnia, headache, and somnolence. As noted above, slow initial titration and monotherapy administration reduce the frequency of side effects.

Thus, FBM should be reserved for treatment of those adults and children with severe epilepsy refractory to other therapies. Those with resistant partial epilepsy that does not respond to other agents or those with resistant broader syndromes, such as Lennox-Gastaut syndrome or myoclonic epilepsy, may benefit from FBM when other agents fail.

Gabapentin
GBP is approved in the United States and throughout the world as adjunctive therapy in the treatment of partial and secondarily generalized seizures in adults. Its use has been extended to increased dosage and monotherapy, and it is now generally used in children, as are all other AEDs shown to be effective for the treatment of partial seizures in adults. GBP was the first of the new AEDs to be extensively tested in children of all ages older than 1 month to demonstrate efficacy and safety in children with refractory and benign syndromes of partial epilepsy. Although synthesized as an analogue of GABA, it may produce its anticonvulsant action through various other mechanisms. Initial clinical trials demonstrated a ≥ 50% reduction in seizures in about 25% of adult patients who received dosages between 1,200 and 1,800 mg/d as adjunctive therapy. Subsequent clinical experience and investigations have shown increased efficacy with increasing doses of GBP as adjunctive or monotherapy, extending the dosage to 6,000 mg/d or above. The initial recommendation for daily dosages in adults of 1,200 to 1,800 mg now seems too low for many patients, and a range of 2,400 to 4,800 mg/d seems more appropriate for those with refractory partial
seizures. In children, initial studies were performed using 20 to 30 mg/kg/d, but as has been seen in adults, increased dosing to at least 60 to 100 mg/kg/d should be considered in those who continue to have refractory partial seizures.

GBP does not bind to plasma proteins and crosses the blood-brain barrier in concentrations similar to those in plasma. It has no metabolism, does not induce hepatic microsomal enzymes, and does not interact with other drugs. This lack of interaction makes GBP an AED of choice in the treatment of patients on multiple other medications, whether for the treatment of epilepsy or for other medical conditions. Renal clearance is linearly related to creatinine clearance, and the elimination half-life is estimated to be between 5 and 9 hours. Initial GBP dosing recommendations for adults are to begin with 300 mg/d, 1,600 mg taken in two divided doses on day 2, and 900 mg in three divided doses on day 3. Titration is then continued rapidly to reach approximately 1,200 to 1,800 mg. Many tolerate 900 mg GBP on day 1, but in some patients, transient neurotoxicity occurs with more rapid dose escalation. The side effects of GBP are generally mild and transient, including drowsiness, fatigue, somnolence, and occasional weight gain. A relatively rarely noted adverse effect is the exacerbation of myoclonic seizures in those who most likely have primary generalized epilepsy. Neurotoxic adverse effects tend to increase with dosage escalation. Positive effects on mood and adjustment are seen to the greatest degree with low-dose GBP. Irritability, temper outbursts, aggressive behavior, and dysphoria have been reported and may be more frequent in mentally retarded children and adults. Although hyperactivity and aggression have been noted in some children, few have required discontinuation of drug because of these side effects.

GBP is the easiest new AED to use because of its lack of pharmacokinetic interactions and the ability to perform dosage titrations relatively rapidly. Because of its properties, GBP may have substantial advantages for treatment of the elderly, women, children, those with multiple handicaps, and those receiving concomitant therapy for other disease states. It has been shown to be very effective in the treatment of neuropathic pain. No life-threatening adverse events are dizziness, diplopia, ataxia, nausea, amblyopia, and somnolence. Overall rash occurred in 10% of patients taking LTG during trials. This overall rash rate is similar to that associated with CBZ. Numerous reports have cited the observation that patients seem more alert when treated with LTG, whereas it has been helpful in other patients. It has not consistently demonstrated efficacy in the treatment of infantile spasms.

The monotherapy studies, when combined, demonstrate that the tolerability of LTG was approximately twice that of PHT and CBZ when assessed by comparing withdrawal rates for adverse effects. The most frequently cited adverse events are dizziness, diplopia, ataxia, nausea, amblyopia, and somnolence. Overall rash occurred in 10% of patients taking LTG during trials. This overall rash rate is similar to that associated with CBZ. Numerous reports have cited the observation that patients seem more alert when treated with LTG. In some children, mild appetite suppression and insomnia have been reported. Some encephalopathic children become hyperactive as they brighten.

The significance of potentially serious rash associated with the use of LTG has resulted in special labeling because of this potentially fatal complication. Stevens-Johnson syndrome and toxic epidermal necrolysis are two related seri-

Lamotrigine

LTG is a chemically unique compound with anticonvulsant potential against numerous seizure types. It appears to block the release of glutamate through stabilization of the presynaptic membrane by blocking voltage-dependent sodium channels, but additional mechanisms of action may well be responsible for its broad range of clinical efficacy. Placebo-controlled studies have demonstrated LTG's efficacy as add-on medication in partial seizures and in the treatment of Lennox-Gastaut syndrome. In addition, LTG is commonly used for the treatment of other primary generalized epilepsy in both adults and children.

The pharmacokinetic profile of LTG indicates that it has a peak plasma concentration achieved in 1 to 3 hours and a volume of distribution in adults of 1.0 to 1.3 L/kg. Plasma protein binding is approximately 55%, thus having no clinical significance. The drug is eliminated through urinary excretion in the form of two glucuronide compounds, with an additional portion of the drug eliminated as the unchanged parent drug. Although LTG has few interactions on other agents, its clearance is influenced by concomitant AEDs. The half-life of LTG is 25.4 hours in adults, when administered alone, but is shortened to 14 hours if the patient receives other AEDs that induce hepatic enzymes. VPA inhibits glucuronidation and prolongs the half-life to a mean of 59 hours. A half-life of ≤ 10 hours is seen in children younger than 12 years who are taking enzyme-inducing drugs, 15 to 26 hours in children taking combined VPA and enzyme-inducing drugs, and 44 to 94 hours in children taking only VPA with LTG. These pharmacokinetic properties must be remembered as cotherapy is added or removed throughout the course of epilepsy treatment.

The efficacy of LTG against refractory partial epilepsy was demonstrated in multiple double-blind, add-on, placebo-controlled studies, with an overall 50% reduction in approximately 25% of patients. Monotherapy studies comparing LTG to PHT and CBZ revealed the similar or slightly superior efficacy of LTG. Studies in children with Lennox-Gastaut syndrome and refractory partial seizures show similar efficacy. An exacerbation of myoclonic seizures has been noted in some children and adults treated with LTG, whereas it has been helpful in other patients. It has not consistently demonstrated efficacy in the treatment of infantile spasms.

The monotherapy studies, when combined, demonstrate that the tolerability of LTG was approximately twice that of PHT and CBZ when assessed by comparing withdrawal rates for adverse effects. The most frequently cited adverse events are dizziness, diplopia, ataxia, nausea, amblyopia, and somnolence. Overall rash occurred in 10% of patients taking LTG during trials. This overall rash rate is similar to that associated with CBZ. Numerous reports have cited the observation that patients seem more alert when treated with LTG. In some children, mild appetite suppression and insomnia have been reported. Some encephalopathic children become hyperactive as they brighten.

The significance of potentially serious rash associated with the use of LTG has resulted in special labeling because of this potentially fatal complication. Stevens-Johnson syndrome and toxic epidermal necrolysis are two related seri-
ous cutaneous disorders that may be part of a single spectrum. Less than 5% of cases of Stevens-Johnson syndrome are fatal, but the estimated mortality of toxic epidermal necrolysis is 30%. These cutaneous reactions may also be accompanied by symptoms suggestive of hypersensitivity, with multiorgan involvement. Initially, rash appeared during the first few weeks of treatment, and, in most cases, it was self-limited, whether or not treatment continued. Subsequently, potentially fatal rashes of the type described above led to an estimate that hospitalization for rash had occurred in approximately 1 per 1,000 adult patients. Patients who had a history of allergy to any drug before LTG treatment had a 2.8-fold increased risk of discontinuation due to rash or fever, whereas patients with a history of allergy to AEDs had a 3.9-fold increased risk. In children the rash rate is higher, approximately 1 in 200 to 1 in 100. Most rashes, however, are benign and promptly resolve on discontinuation of treatment. Mortality from rash is extremely rare and, on the basis of worldwide estimated exposures and spontaneously reported deaths recently attributed to rash, is approximately 1 in 100,000. LTG-associated rash almost entirely occurs within the first 8 weeks of exposure. Unfortunately, mild rash may progress to severe rash. Three factors may increase the risk of rash: (1) the patient’s age, (2) cotherapy with VPA, and (3) the rate of dose escalation. It is, therefore, suggested that physicians do not exceed the manufacturer’s dosing guidelines and that they follow particular attention to whether the patient is receiving VPA.

Patients and their families must be educated about rash as they will be the first to determine this symptom. It is highly recommended that a patient be seen urgently and that LTG be stopped if there is not an alternative explanation for the patient’s rash. Slow titration of dosing and removal of VPA from the patient’s AED regimen may well decrease the overall rash rate and, most importantly, the potentially serious rash. Rapid titration is not recommended. Recent data confirm the success of this strategy.

LTG is a very useful addition to the armamentarium of AEDs used in the treatment of partial and other generalized seizure types. It is frequently used as initial monotherapy. Favorable pharmacokinetics and efficacy and its nonsedating properties should be balanced by its rash risk and titration schedule.

Levetiracetam

LTG is a pyrrolidine derivative with antiepileptic properties. Its antiepileptic effect does not derive from any known mechanism involved in inhibitory and excitatory neurotransmissions. However, a brain-specific binding site has been demonstrated in synaptic plasma membranes, and the drug shows efficacy in a kindling model of epilepsy. LTG is rapidly and almost completely absorbed after oral administration and is not affected by food. LTG is not protein-bound and its metabolism is not cytochrome P-450 dependent, with 66% of the dose renally excreted unchanged. The pharmacokinetics are linear, with peak plasma levels at 1 hour after administration and a plasma half-life of 6 to 8 hours, yet dosing can be successful twice daily.

There have been three multicenter, double-blind, multinational studies in adult patients with partial-onset seizures. In the first, LTG was compared as an add-on therapy at 3,000 mg/d and 1,000 mg/d with placebo in 293 patients. A responder was defined as having a > 50% decrease in seizures. Response rates of 39.8%, 33%, and 10.8% were seen in the 3,000 mg and 1,000 mg groups of levetiracetam and placebo, respectively. The second trial was a multinational European trial that enrolled 322 patients who were assigned either to treatment groups of 2,000 mg/d or 1,000 mg/d of LTG or to a placebo arm. Following a 4-week titration and a 12-week treatment phase, good efficacy also was demonstrated with the higher-dosing group, with a responder rate (> 50% seizure reduction) of 30.9% and a responder rate of 22.8% in the lower-dosing group. A response rate of 11.2% was seen in the placebo group. In the third study, LTG was started as add-on followed by a monotherapy treatment period. The study involved 261 patients, with 171 randomly assigned to 3,000 mg/d and 90 randomly assigned to a placebo control group. In the treatment group, responder rates as defined above were 42.1% during the add-on phase and 59.2% in the monotherapy phase. Combined (for all three trials in 904 patients), efficacy rates were 12.6%, 27.7%, 31.6%, and 41.3% for placebo, 1,000 mg, 2,000 mg, and 3,000 mg LTG, respectively.

Although formal trials continue, LTG use in children has increased. In one open-label trial in 24 patients aged 6 to 12 years, LTG was started at 10 mg/kg/d divided into two doses and titrated to 40 mg/kg/d. Twelve of 24 achieved a > 50% response rate. Applicability to other seizure types is currently being investigated. Dosing in children is approximately one-third higher on a mg-per-kg basis than in adults.

LTG is well tolerated and has a good safety profile. The most common adverse events were asthenia (32.4%), somnolence (19.2%), and dizziness (18.7%). These were considered minor, and 79.6% improved. No potentially life-threatening complications were seen. In children, similar adverse effects were reported, along with nervousness. This post-marketing experience with LTG has identified behavioral reactions characterized by hyperactivity and aggression, with rare reports of psychosis. All were reversible with discontinuation and in many instances pretreatment reactions or diagnoses placed these individuals at higher risk for these behavioral manifestations. The role of LTG in pediatric and adult epilepsy is still evolving, with reports
of success against a broader spectrum of seizure types, including generalized epilepsy, such as juvenile myoclonic epilepsy (JME). Its potential effect on altering epileptogenesis because of its effect in the kindling model makes it an attractive AED to use early in childhood. Controlled studies are under way in both partial seizures and other types of epilepsy.

Oxcarbazepine

OXC is a homologue of CBZ. It was developed as an alternative to CBZ for patients who had adverse reactions to CBZ or PHT. OXC is the 10-keto derivative of CBZ. It is not metabolized into a 10,11 epoxide, leading to improved tolerability. OXC is similar to CBZ in its mechanisms of action and has its antiepilepsy effect through its active metabolite 10,11-dihydro-10-hydroxy-5H-dibenz(\(bf\)) azepine-5-carboxamide (monohydroxy derivative). Most of the clinical development took place during the early 1990s, though use in several countries dates back more than 15 years.

Typical dosing is recommended to start at 300 mg/d in adults, increasing to 900 to 1,200 mg/d, though it has been effectively increased to 3,000 mg/d. Typical dosing in children is 10 mg/kg/d, advanced to a mean dosage of 60 mg/kg/d. Early experience with OXC suggests that starting at half the initial recommended dose (i.e., 150 mg/d in adults or 5 mg/kg/d in children) may lead to better tolerability. Absorption is about 95% following oral intake, and peak concentrations are reached within 4 to 6 hours. OXC is 38% protein bound. The plasma half-life is 8 to 13 hours and linear.

Numerous studies have been carried out using OXC both as adjunctive and monotherapy in adults and children. In one early trial, OXC was compared with CBZ in an add-on, randomized, crossover trial in 40 adult patients. Mean dosages for CBZ were 500 to 2,000 mg/d and 900 to 3,600 mg/d with OXC. No difference in efficacy was seen.

In the Scandinavian multicenter trial, 235 drug-naïve patients with newly diagnosed epilepsy were randomized to treatment with either OXC or CBZ. The study comprised patients with partial seizures with or without secondary generalization. In both groups, more than 80% of the patients experienced at least 50% seizure reduction with no significant difference in the two treatment arms. However, with regard to toxicity, a significant difference in favor of OXC was demonstrated, with a higher number of patients stopping CBZ.

A recent study looked at OXC in children younger than 7 years of age, including a 7-month-old infant. A mean maximum dose of 50 mg/kg/d (range, 21 to 86 mg/kg/d) was reported. Thirty-three of 53 patients had a > 50% seizure reduction, and 12 of 44 with a focal-onset seizure became seizure free.

The most commonly reported side effects are tiredness, headache, dizziness, and ataxia. The side-effect profile is very similar for OXC and CBZ, but the number of side effects seems to be higher with CBZ than with OXC. Skin rash has been seen but is rare, and some patients demonstrating sensitivity to CBZ have not developed a reaction with OXC. OXC treatment is sometimes associated with the occurrence of hyponatremia, probably through regulatory changes in antidiuretic hormone. This effect is mild and reversible, but it increases at doses higher than 25 to 30 mg/kg/d. In those with multiple handicaps with altered fluid intake patterns, hyponatremia may be more frequent. No significant systemic toxicity, such as bone marrow suppression or hepatic failure, has been seen.

This drug possesses an advantage in producing less in toxicity and rashes, making it a welcome addition to the AED armamentarium. CBZ is available in numerous dosing formulations, allowing it to be easily given to children. With the development of these formulations for OXC, this AED will certainly become one of the drugs of choice for the treatment of partial and secondarily generalized seizures.

Tiagabine

TGB is one of two new drugs whose action directly affects the GABA system. By increasing GABA, the primary inhibitory neurotransmitter, seizures are decreased. Barbiturates and benzodiazepines act on the GABA receptor, and VPA is a GABA analogue. Whereas VGB (see below) is an irreversible inhibitor of GABA transaminase, which blocks degradation and therefore increases levels of GABA, TGB consists of nipecotic acid joined to a lipophilic anchor that was designed to block GABA uptake by presynaptic neurons and glial cells. TGB actually binds to a GABA transport protein, thus competing for GABA binding sites in the transporter. Thus, there is an increase in GABA concentrations and duration of action in the synaptic cleft without substantially altering total brain GABA levels. TGB has undergone extensive clinical trials in adults with intractable partial epilepsy and pediatric trials show similar results.

TGB is rapidly absorbed, with peak blood levels achieved within 2 hours. The mean half-life is 4 to 9 hours, but no significant change in efficacy has been demonstrated in clinical trials that evaluated dosing twice or more frequently daily. TGB is metabolized by the hepatic cytochrome P-450 system and is, thus, induced by barbiturates, CBZ, and PHT, but it does not appear to induce or inhibit hepatic microsomal enzyme systems. Although highly protein-bound (over 95%), it does not appear to interact with most commonly used drugs.

Clinical trials in adults suggest that TGB is an effective AED against partial seizures, with a favorable adverse-event profile. When dosages of 16, 32, and 56 mg/d were...
Patients receiving PHT, especially those with higher ther-
zyme-inducing AEDs, such as PB, CBZ, and PHT.

to serum proteins, and few pharmacokinetic interactions
include high bioavailability, a half-life of approximately
24 hours in adults, linear elimination kinetics, low binding
and reducing adjunctive AEDs resulted in a much lower
adverse-effect rate and fewer TPM discontinuations.

adverse events reported with TGB are frequently dose-
related and indicate that side effects are better tolerated
when the drug is started slowly and titrated upward. The
most common adverse events are dizziness, asthenia, and
nervousness. Tremor, diarrhea, depression, and emotional
lability also were noted. Similar findings have been seen in
children. The side effects of weakness and hypotonia have
actually been used to advantage to treat spasticity.
Nonconvulsive status epilepticus has been noted in patients
receiving TGB, but its incidence seems no greater than
that seen in the general epilepsy population. No visual
disturbance secondary to retinal toxicity, as seen in VGB, has
been noted with TGB. Conversion to TGB monotherapy
was associated with positive changes of varying degrees on
psychological tests, whereas continued adjunctive therapy
produced neither positive nor negative changes.

This drug, which is the first available GABA-ergic com-
 pound in the United States, offers a significant difference
in mechanism of action in the treatment of partial seizures,
and controlled studies as well as clinical use show it to be
a relatively well-tolerated agent. TGB’s efficacy as first-line
treatment for patients with partial epilepsy is really
untested. Whether it can be an option for treating infantile
spasms in children unable to receive alternative med-
ications, such as steroids or VGB, is a real consideration.
Also, it may be considered as first-line monotherapy for
patients with partial seizures and spasticity.

**Topiramate**

TPM, a fructopyranose compound, is a structurally novel
AED. It has multiple mechanisms of action. It blocks
seizure spread and elevates seizure susceptibility by acting
on kainate (glutamate) and GABA receptors, sodium chan-
nels, and calcium channels; it appears to have a carbonic
anhydrase inhibitory effect. It is a drug with a broad spec-
trum of activity. The pharmacokinetic properties of TPM
include high bioavailability, a half-life of approximately
24 hours in adults, linear elimination kinetics, low binding
to serum proteins, and few pharmacokinetic interactions
with other drugs. Its clearance, however, is increased by
enzyme-inducing AEDs, such as PB, CBZ, and PHT.
Patients receiving PHT, especially those with higher ther-
apaeutic levels, may experience an increase in PHT levels
from an inhibition of metabolism.

TPM clearance in children is approximately 50%
greater than in adults, so the plasma concentrations of
TPM in children will be approximately 33% lower than
that seen in adults when both are given an identical dose.

TPM is indicated as adjunctive therapy in patients aged
2 to 16 years with partial onset seizures or primary gener-
alyzed tonic-clonic seizures, and in patients 2 years of age
and older with Lennox-Gastaut syndrome. The safety and
efficacy of TPM were demonstrated in six double-blind,
placebo-controlled clinical trials in adults with partial
onset seizures. Adjunctive TPM in dosages ranging from
200 to 1,000 mg/d significantly improved seizure control,
and neurotoxicity was found to be related to the speed of
dosage titration and increased with higher doses. Taking all
studies together, approximately 44% of TPM-treated ver-
sus 12% of placebo patients had a 50% reduction in
seizures. TPM is not indicated as monotherapy in patients
with seizures. A monotherapy trial compared patients
receiving 1,000 mg/d with those receiving 100 mg/d of
TPM. Among patients completing 16 weeks of double-
blind treatment, including 11 weeks of TPM monotherapy,
23% of the high-dose TPM group became seizure free, but
none in the low-dose group achieved this outcome. In an
extension of the above trial, 66% of patients remained
seizure free for > 3 months. Pediatric trials in children
with partial seizures and one combining children and
adults with Lennox-Gastaut syndrome have shown a
broader spectrum of seizures activity beyond partial
seizures and have further demonstrated the safety of this
agent. Its efficacy against absence seizures seems only mod-
erate, but it has demonstrated efficacy in JME.

The most common side effects in adults and children
receiving TPM during controlled trials were dizziness, men-
tal slowing, somnolence, ataxia, fatigue, and fusion-
impaired concentration and paresthesia. Side effects tend
be mild to moderate in severity, prompting discontinuation
in 14% of adult patients receiving TPM versus 3% receiv-
ing placebo. The incidence and severity of side effects is
directly dependent upon scheduled titration, starting dose,
and ultimate dosage of TPM. TPM has also been associated
with weight loss, nephrolithiasis, and paresthesias. Open-
label studies allowing slower titration starting at 25 mg/d
and reducing adjunctive AEDs resulted in a much lower
adverse-effect rate and fewer TPM discontinuations.

At present, the recommended eventual total daily dose
of TPM in adults as adjunctive therapy is 200 to 400 mg/d
in two divided doses. Some patients respond equally well
to doses as low as 100 mg/d; others require higher doses
above 400 mg/d. To control the appearance of adverse
effects, it is recommended that the dose be initiated at 25
to 50 mg/d with weekly titrations of an additional 25 to
50 mg. In most children, initial dosing of 0.5 to 1 mg/kg/d should be followed by titration of approximately equal amounts every 1 to 2 weeks to doses of 4 to 10 mg/kg/d.

In summary, TPM appears to be an extremely potent new AED with a broad spectrum of antiseizure activity. Its side effects may be substantially reduced by proper dosing and careful dose titration at the onset of therapy. Although its interactions are few, patients on high-dose PHT should be clinically monitored because of an interaction that may inhibit the metabolism of PHT, with resultant toxicity as PHT levels rise. The full impact of this agent is still being realized, but it appears to be a major AED with broad-spectrum potential that some are now considering a first-line therapy. No hypersensitivity or idiosyncratic reactions have been associated with TPM.

**Vigabatrin**

VGB is an amino acid that is highly water soluble and acts intracellularly as an irreversible inhibitor of GABA transaminase, thus allowing increased GABA levels to be present at GABA-binding sites and allowing increased inhibitory neurotransmission. Although its serum half-life is only 5 to 7 hours, its effective half-life is much longer, as it irreversibly binds to the enzymatic site. VGB does not appear to interact significantly with most other AEDs because it is not metabolized and is excreted unchanged in the urine. At a dose of 50 mg/kg, VGB causes a 200 to 300% increase in GABA in the cerebrospinal fluid (CSF) and brain tissue. A reduction of VGB dose in adults from 3 g/d to 1.5 g/d results in a proportional reduction of GABA concentrations in the CSF. However, there does not seem to be a direct relationship between efficacy and percentage increase in GABA in the CSF. Development of VGB in the United States was delayed because of the presence of intramyelinic vacuolization and edema in specific areas of rodent and canine brains. These effects were reversible when VGB was stopped. More recently, visual field changes secondary to retinal toxicity have been reported in more than 30% of those treated.

The efficacy of VGB against partial seizures has been assessed in multiple studies in adults and children. Remarkable response rates (50% reduction) in adults receiving 2 to 3 g/d of vigabatrin as add-on therapy in double-blind, placebo-controlled studies revealed response rates ranging from 33 to 64%. VGB is most effective against partial seizures but may exacerbate myoclonic seizures.

Numerous studies have demonstrated similar data for pediatric partial seizures, but perhaps the most exciting reports have come from trials on the treatment of infantile spasms, where VGB has shown superior results, especially in children with tuberous sclerosis. Results of trials with children and adults with Lennox-Gastaut syndrome are less encouraging.

Sedation and fatigue are the adverse effects most commonly reported in clinical trials, followed by dizziness, weight increase, agitation, abnormal vision, amnesia, and nystagmus. Depression, confusion, and other behavioral abnormalities have also been reported. A small number of patients have developed psychoses. In children, hyperactivity and agitation are reported in up to 50% of patients, especially when high doses of VGB are administered.

VGB is commonly administered once or twice daily, beginning with 500 to 1,000 mg daily and increasing by approximately 500 mg weekly, up to 3 g or 50 mg/kg/d for the treatment of partial seizures. Very young children with infantile spasms frequently receive doses in excess of 100 mg/kg/d.

The further development of VGB in the United States has been delayed because of its toxicity profile, but its effect in infantile spasm remains superior.

**Zonisamide**

ZNS is chemically similar to indole. ZNS has been demonstrated to affect voltage-dependent sodium channels as well as block T-type calcium channels. ZNS is rapidly and almost completely absorbed. Peak levels are achieved in about 3 hours. Protein binding is 50 to 60% in humans. ZNS has a half-life of 50 to 68 hours and is extensively metabolized. The drug undergoes reductive biotransformation to the open ring metabolite 2-sulfamoylacetylphenol. Typical starting dose in adults is 100 mg/d and in children 1 to 2 mg/kg/d twice or three times daily. Maintenance is typically 200 to 600 mg/d in adults and 4 to 10 mg/kg/d in children.

The drug’s efficacy was evaluated initially in adults with partial complex seizures. These studies yielded very similar results, with 29 to 30% achieving > 50% seizure reduction. Studies comparing the efficacy of CBZ for partial seizures and of VPA for generalized seizures showed similar efficacy. Early reports of ZNS efficacy in myoclonus are of particular interest to practitioners treating children with epilepsy. Though numbers are small, responses have been seen in patients with Baltic myoclonus and other patients with progressive myoclonic epilepsy, myoclonic epilepsy with ragged-red fibers, and severe myoclonic epilepsy of infancy.

ZNS is a preferred AED for the treatment of JME in Japan, but not for childhood absence epilepsy. Growing evidence demonstrates ZNS efficacy in infantile spasms. Open studies in both Japan and the United States have demonstrated approximately two-thirds of children for whom other therapies have failed have become spasm free. Initial elevated dosing of 5 to 10 mg/kg/day is recommended. Lethargy and irritability are the most common adverse effects in these infants.

Overall, adverse events reported were somnolence, ataxia, anorexia, confusion, and abnormal thinking, with the incidence rate significantly higher in the ZNS group than in placebo group (92 versus 58% and 59 versus 28%,
respectively). Discontinuation rates because of adverse events in the U.S. studies were 14% in the ZNS group and 1% in the placebo group. In the European studies, the discontinuation rate because of adverse events was 3% in the ZNS group; there were no discontinued cases in the placebo group.

In further studies, 13 of 505 patients developed nephrolithiasis. Ten of the 13 patients had positive histories of renal calculi or urinary tract abnormalities. The following adverse events were reported: Stevens-Johnson syndrome, Lyell’s syndrome, agranulocytosis, and acute renal failure. A small number of patients with hyperthermia associated with decreased sweating (oligohydrosis) has been reported. These individuals are almost all children or mentally retarded adults. Adequate hydration leads to recovery without drug discontinuation.

The role of ZNS in the treatment of pediatric epilepsy is still evolving. Certainly, if results in myoclonic seizures and infantile spasms hold true, this drug will receive much wider use in the pediatric population than its current adjunctive indication for partial seizures in adults. Although new in the United States, ZNS is considered to be the drug of choice in Japan for the treatment of certain generalized seizure syndromes, such as JME.

**A Rational Approach to Treatment**

With numerous agents now available for the treatment of epilepsy, one needs to consider which is best for the individual patient. As shown in Figure 21-1, the selection of the first-choice drug should be made on the basis of a patient’s seizure type or types. Unfortunately, the initial clinical studies designed for the licensing of new compounds rarely give sufficient information to establish the ultimate dosing and use characteristics that will be determined after long-term use in much larger populations of patients. Furthermore, comparative studies that have evaluated a number of the new AEDs frequently employ strategies for starting doses of medication, titration schedules, and restrictions on dosage alterations that do not reflect typical clinical practice. Thus, although these studies are valuable, they may not be absolutely clinically relevant. Meta-analysis studies also give information of comparative value by determining odds ratios for 50% responders, the likelihood of withdrawal, and the number needed to be treated to find the responder. Unfortunately, confidence intervals do not allow a true separation of agents. The pitfalls of meta-analysis studies are such that they can be used only to a certain degree.

Perhaps a starting point for the selection of initial AED therapy would be to consider which drugs may be considered first-line monotherapy for specific epilepsy types. For partial seizures, all the classic AEDs (CBZ, PHT, PB, primidone, and VPA) have been shown to be useful. The side-effect profiles and experience using each agent may well determine the drug of choice for individual physicians and patients. Such issues as risk factors for idiosyncratic effects because of a prior drug reaction, likelihood of weight gain or weight loss, and likelihood of developing behavioral side effects (eg, irritability, hyperactivity, lethargy, or potential effects on cognition) will certainly be factored into the equation. For this reason, most patients will not receive a barbiturate as a first-line drug. Of the newer AEDs, reports support the use of GBP, LTG, TPM, OXC, TGB, ZNS, or FBM as monotherapy. Nearly all would be appropriate for the treatment of partial seizures. One might ask whether most patients who were previously considered for treatment with CBZ should now be started on OXC because of its potential for decreased deleterious effects. For generalized seizures seen in children, ESX and VPA remain the two most widely used AEDs for the treatment of absence seizures; LTG has been demonstrated to have good antiepileptic activity and also should be considered as first-line therapy in some individuals. The titration schedule for LTG and the relatively rare occurrence of rash when used as monotherapy at a proper titration rate will certainly influence the choice of this agent sooner or later.

Similarly, adverse effects of VPA and ESX must be balanced. In the treatment of generalized symptomatic epilepsies, such as Lennox-Gastaut syndrome, FBM demonstrated the highest degrees of adequacy against atonic seizures, but its toxicity profile, even though young children seem to be the least at risk, make it a fourth- or fifth-line drug. First choices for Lennox-Gastaut syndrome include VPA and, more recently, LTG and TPM. LTG tends to be a better agent against absence seizures, whereas TPM in our clinical experience does not demonstrate the exacerbation of myoclonic type seizures seen with LTG.

A balance between potential serious adverse effects and idiosyncratic reactions and efficacy is probably the leading factor in determining the drug of choice for monotherapy. If the first drug is unsuccessful, a second monotherapy trial should be undertaken. Just as with the first-choice drug, the adverse effects associated with the second-choice drug—including cosmetic, weight gain, and women’s issues, and the likelihood of behavior changes or neurotoxicity—also must be considered. Table 21-2 depicts a suggested approach to sequencing the choice of AEDs.

The ultimate question is whether a “drug of choice” is truly established for every patient with epilepsy. Certainly, individual patient characteristics will determine some choices. Data reveal slightly increased efficacy of one agent over another but do not clearly place one of the new or classic AEDs as the drug of choice for all patients. In selecting the drug of choice for the individual patient with
TABLE 21-2. Rational Sequencing of Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Efficacy appropriate for broad spectrum of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial onset</td>
</tr>
<tr>
<td>Primary generalized tonic-clonic</td>
</tr>
<tr>
<td>Encephalopathic generalized</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Children (all ages)</td>
</tr>
<tr>
<td>Mechanisms of action</td>
</tr>
<tr>
<td>No evidence of therapeutic tolerance</td>
</tr>
<tr>
<td>Favorable safety profile</td>
</tr>
<tr>
<td>Idiosyncratic</td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Well tolerated with dose-management techniques</td>
</tr>
<tr>
<td>Monotherapy, whenever possible</td>
</tr>
</tbody>
</table>

epilepsy, seizure type, epilepsy syndrome, pharmacokinetic parameters, ease of use, and, above all, drug tolerability and lack of adverse effects should be considered. Effects on comorbid conditions, positive or negative, also must be considered. New and established AEDs must all be considered when selecting the first-choice AED.

Suggested Readings


Practitioner and Patient Resources

Epilepsy Foundation
4351 Garden City Drive, Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or (800) EFA-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation will ensure that people with seizures are able to participate in all life experiences and will prevent, control, and cure epilepsy through research, education, advocacy and services.

The Epilepsy Foundation of New Jersey
2150 Highway 35 North, Suite 207-C
Sea Girt, NJ 08750
Phone: (732) 974-1144 or (800) 372-6510
E-mail: fschn@aol.com
http://www.efnj.com
The Epilepsy Foundation of New Jersey is dedicated to the education and support of people with developmental disabilities including epilepsy, cerebral palsy, autism, mental retardation, spina bifida, and traumatic brain injury, their families, caregivers, and health care professionals.