ABSTRACT

Selection of an antiepileptic drug (AED) for initial treatment of epilepsy in infancy, childhood, and adolescence should ideally be made after a clear diagnosis of the patient's epilepsy because a common cause of failure of the first AED is misdiagnosis. However, AED efficacy data based on placebo-controlled, double-blinded, randomized clinical studies are unavailable for many childhood syndromes. In these cases, agent selection must be based on the best available data.

Choice of an AED for the treatment of epilepsy in infants and children depends not only on the efficacy of the agent but also on safety, impact on behavior and learning, and existing patient comorbidities. Neuropsychiatric comorbidities in children with epilepsy include attention-deficit/hyperactivity disorder, autistic spectrum disorders, depression, anxiety, and thought disorders. Any of these problems may be worsened or improved by specific AEDs. In addition, the effect of AEDs on body weight, insulin sensitivity, lipid profile, and bone health is becoming better appreciated, and newer AEDs may offer significant advantages regarding metabolic impact. However, a continuing need remains for the development of newer AEDs that are targeted for the developing brain and will improve efficacy and tolerability of treatment in childhood epilepsy.

The following information is based partially on a review that appeared as a supplement to the November 2004 issue of the journal Neurology, and is motivated in part by recent guidelines established by the American Academy of Neurology (AAN) and the American Epilepsy Society (AES). This article describes general principles for selecting appropriate pharmacotherapy for children with epilepsy and offers an approach to using the new antiepileptic drugs (AEDs) versus the older agents.

GENERAL PRINCIPLES FOR SELECTING PHARMACOTHERAPY

Accurate diagnosis is essential in selecting appropriate pharmacotherapy for the child with epilepsy. Misdiagnosis is also a significant problem in the adult population, occurring in nearly 33% of adults diagnosed with complex partial seizures. Appropriate diagnosis is extremely important, as it is likely that children will fail treatment with the first therapeutic agent if their epilepsy syndrome has been misdiagnosed. Physicians must be aware of age-specific treatment concerns in children, as AEDs may have age-specific toxicities such as cutaneous, gingival, and hematologic reactions and hepatotoxicity. Neurobehavioral and cognitive effects of treatment are also of paramount concern because they may impact a child's learning and social development.

Furthermore, physicians must be aware of psychiatric and neurocognitive comorbidities and able to distinguish these conditions from treatment-emergent behavioral and cognitive adverse effects. For example, depression may exist with epilepsy as a comorbidity, but it can also be a treatment-emergent adverse effect of barbiturate therapy. Comorbidities in children with epilepsy comprise a wide range of conditions, includ-
ing depression, anxiety, attention deficit disorder, thought and communication disorders, autism spectrum disorders, and migraines.1,2

A recent review of the mechanisms of action of common AEDs and their relevance to drug-related neurobehavioral adverse effects indicates that medications with gamma-aminobutyric (GABA)-ergic mechanisms are associated with the most detrimental effects on cognition by impairing attention, whereas those mechanisms that act primarily at sodium channels have minimal effect on cognition. Levetiracetam, which has nonconventional GABA-ergic and calcium channel effects, has positive effects on cognition in animals (however, there is rapidly accumulating evidence that this drug has adverse effects on mood and cognition in humans, especially in children). The antiglutamatergic drugs may interfere with the consolidation of learning and memory, but they are known to provide neuroprotection in addition to their anti-seizure effects.

The findings of a recent meta-analysis of neurobehavioral and psychiatric effects of commonly used AEDs further demonstrate that treatment with phenobarbital is associated with higher rates of negative behavioral effects and depression than are other therapeutic agents.1 Depression has been well documented during treatment with barbiturates, benzodiazepines, and phenytoin. Therefore, phenobarbital is not recommended for use as an initial monotherapy in children with epilepsy. Also, despite widespread anecdotal impressions to the contrary, data from the same meta-analysis indicate that lamotrigine, zonisamide, levetiracetam, and topiramate are associated with comparable rates of negative behavioral effects and depression in children treated for epilepsy (Table 1).1

Weight gain is an adverse effect of significant concern in patients treated with valproate, gabapentin, or carbamazepine, whereas weight loss is associated with felbamate, topiramate, and zonisamide. Endocrinopathies and altered insulin sensitivity may occur with valproate. With regard to dyslipidemias, a significant number of existing publications document the elevation of total cholesterol, low-density lipoprotein (LDL), and ratios of LDL to high-density lipoprotein (HDL) or total cholesterol to HDL in children and adults treated with phenobarbital, phenytoin, and carbamazepine. There are also concerns regarding bone health with traditional agents, and agents that induce the hepatic microsomal system also tend to dramatically reduce serum levels of statins. Cognitive and neurobehavioral effects may occur with topiramate, and behavioral effects may occur with zonisamide and levetiracetam, but lamotrigine may induce fewer adverse effects on a patient’s cognition and behavior. As attention-deficit disorder is a common comorbidity in children with epilepsy, physicians must understand that psychostimulants can be used safely and effectively in these children and may actually improve electroencephalography findings over time.1,4

**EXISTING TREATMENT GUIDELINES**

Treatment guidelines regarding efficacy and tolerability of new antiepileptic agents in the treatment of new-onset epilepsy and refractory epilepsy were pub-

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Negative Behavioral Effects*</th>
<th>Psychiatric Side Effects†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Depression</td>
<td>psychosis</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Negative behavior: — = rare or not reported; + = 1%–20%; ++ = 21%–40%; +++ = >40%.
Psychiatric side effects: — = rare or not reported; + = 1%–4%; ++ = 5%–10%; +++ = >10%.

*Behavioral event frequencies are based on a weighted average calculated over all studies. For studies that did not report an overall behavioral adverse event rate, the highest rate reported for any single behavioral event was used. For studies that only reported behavioral event rates for events that caused drug discontinuation or dosage reduction, these rates were used. Somnolence was not considered a behavioral event when calculating frequencies from single events. However, some studies included somnolence in the overall behavioral event incidence rate.

†Frequencies reported are not weighted averages but reflect the actual incidence rates from studies that reported psychiatric events.

lished jointly in 2004 by the AAN and the AES.\textsuperscript{5,6} Table 2 briefly summarizes key points of these guidelines in the treatment of new-onset epilepsy.\textsuperscript{5} AAN-approved evidence-based recommendations for monotherapy in patients with newly diagnosed partial/mixed seizures include oxcarbazepine (an agent approved by the US Food and Drug Administration for this indication) and gabapentin, lamotrigine, and topiramate (which are not yet approved for this indication). Gabapentin, lamotrigine, and topiramate were judged by the AAN/AES joint panel to provide acceptable therapy based on evidence from existing clinical studies. Based on the same criteria, the joint panel also stated that lamotrigine may be used in newly diagnosed absence seizures.

The companion guidelines for treatment of refractory epilepsy state that levetiracetam and zonisamide are acceptable adjunctive treatments for patients with partial seizures but are not acceptable for initial monotherapy in these patients (Table 3).\textsuperscript{6} Topiramate and lamotrigine received the widest endorsements, although lamotrigine is not recommended for primary generalized seizures involving generalized tonic-clonic seizures because its effect is established mainly against absence seizures. Topiramate was given a broad endorsement, although in the treatment of primary generalized seizures the guidelines refer only to generalized tonic-clonic seizures. The efficacy of topiramate against absence seizures has not been demonstrated convincingly. Therefore, topiramate and lamotrigine are new agents with broad applicability.

Based on the evidence, topiramate was recommended most often for the treatment of generalized tonic-clonic seizures in adults and children. In addition, topiramate and lamotrigine may be used to treat atonic episodes, although lamotrigine and gabapentin occasionally worsen the myoclonic seizures that can be part of the Lennox-Gastaut syndrome.

**Pharmacotherapy in Selected Epilepsy Syndromes**

**Neonatal Seizures**

Phenobarbital and phenytoin continue to be used as the first-line agents in the treatment of neonatal seizures, but offer effective treatment in less than 50% of these patients when used as monotherapy. The drugs are effective in only 60% of patients when used together.\textsuperscript{7} A great deal of interest has been shown in using topiramate for neonatal patients with seizures, and anecdotal support exists for the use of this agent when enteral administration is possible.

A recent study identified that a large number of commonly used drugs, including phenytoin, pheno-

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**Table 2. Summary of AAN-Approved Evidence-Based Guidelines Level A or B Recommendations for Use in Treatment of Patients with New-Onset Epilepsy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Newly Diagnosed New-Onset Epilepsy</th>
<th>Newly Diagnosed Absence Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Not US Food and Drug Administration approved for this indication.

AAN = American Academy of Neurology.

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**Table 3. Summary of AAN-Approved Evidence-Based Guidelines Level A or B Recommendations for Use in Treatment of Patients with Refractory Epilepsy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Partial/Adjunctive Monotherapy</th>
<th>Partial Monotherapy</th>
<th>Primary Generalized</th>
<th>Symptomatic Generalized</th>
<th>Pediatric Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Not US Food and Drug Administration approved for this indication.

AAN = American Academy of Neurology.

Reprinted with permission from French et al. Epilepsia. 2004;45:410-423.\textsuperscript{6}
barbital, diazepam, clonazepam, vigabatrin, and valproate, cause widespread apoptosis in the developing rat brain.8 The clinical importance of this finding remains unclear because during organogenesis in the developing human brain there is an overexpression of cells that subsequently undergo programmed cell death. Thus, it is unknown whether this observation represents de novo brain injury or an acceleration of this normal apoptotic process—a question that must be answered by future longitudinal studies. However, subsequent work by some of the same investigators found that topiramate does not appear to induce this same apoptotic effect.9 In general, the mechanism by which topiramate works, selective non-NMDA glutamate blockade or AMPA receptor blockade, may be the least toxic method to treat seizures in the immature brain and has the potential to be protective.

FEBRILE CONVULSIONS

In the United States, febrile convulsions occur with a 2% to 4% frequency in as many as 100 000 children each year. Seizures can be prolonged, and prolonged seizures are associated with an increased risk of recurrence. Seizures that do not stop naturally in 5 to 10 minutes are unlikely to stop without definitive intervention.10-12 It is well known that delay in seeking treatment for prolonged seizures reduces the sensitivity of GABA receptors to drug treatment, presumably because of receptor internalization. Therefore, early treatment intervention and the prevention of future events is of key importance for children with febrile seizures. Phenobarbital and valproate generally are not chosen for this syndrome because of potential toxicity and cognitive consequences; phenytoin and carbamazepine are ineffective for this problem. Diazepam is effective at 0.33 mg/kg administered orally 3 times daily and administered intermittently during febrile illnesses. The most effective approach to handling a patient’s recurrent febrile seizures is the administration of rectal diazepam gel if the seizures do not stop spontaneously after 5 to 10 minutes. In this method, definitive treatment can be administered by parents at home before taking the child to the emergency room.

ROLANDIC EPILEPSY

Rolandic epilepsy is a common and interesting syndrome of childhood, although surprisingly limited data are available from American studies. The carbonic anhydrase inhibitor sulthiame offers effective treatment14 and is used quite widely to treat this syndrome in Europe, but it is unavailable in the United States. Based on evidence from a double-blind, placebo-controlled study, gabapentin is the treatment of choice in the United States.15 Carbamazepine is also used quite commonly in the United States, but it can be associated with detrimental effects on memory.16

CHILDHOOD ABSENCE EPILEPSY

The classic medication for childhood absence epilepsy in the United States has been ethosuximide, although it may allow generalized tonic-clonic seizures in susceptible patients. Valproate is an alternative agent, used alone or in combination with ethosuximide for patients with refractory seizures. However, physicians must be aware that this combination should be pursued cautiously because valproate may raise ethosuximide concentrations to possibly toxic levels. Lamotrigine offers effective treatment and is nonse-dating. However, good data to compare these 3 agents do not exist, although a large study commissioned by the National Institutes of Neurologic Disorders and Stroke will soon compare the drugs’ efficacy, pharmacokinetics, pharmacodynamics, pharmacogenomics, and neurocognitive functioning effects. Data also suggest that levetiracetam may be useful in the treatment of generalized spike-waves.18 Physicians must recognize how to treat childhood absence seizures and be aware of agents that should not be used. Healthcare providers must understand that phenytoin, carbamazepine, tiagabine, and probably gabapentin and vigabatrin will exacerbate absence seizures and should be avoided.

JUVENILE MYOCLOTONIC EPILEPSY

Valproic acid is the criterion standard in treating juvenile myoclonic epilepsy and is generally considered the most effective agent for controlling all of the phenotypic expressions of this syndrome, including myoclonic seizures (particularly upon awakening), in addition to grand mal and absence seizures.19,20 New agents continue to be explored because of concerns regarding the link between valproic acid and weight gain, in addition to other toxicities. Lamotrigine may be useful, particularly in treating absences seizures, whereas topiramate may be effective with generalized tonic-clonic seizures, and anecdotal evidence suggests that lamotrigine and topiramate may exert significant synergy, in animal models and in humans.21
PARTIAL SEIZURES
A considerable number of patients with partial seizures, particularly those patients with hippocampal sclerosis or dual pathology, fail to respond to most treatment agents. According to the AAN/AES recommendations, oxcarbazepine and topiramate are the new-generation drugs that can be used as initial monotherapy for refractory partial epilepsy. In these recommendations, lamotrigine received a limited endorsement for use as a monotherapy, based on available clinical data. Currently, insufficient evidence exists to recommend gabapentin, levetiracetam, tiagabine, or zonisamide as monotherapy for this syndrome.

INFANTILE SPASMS
Infantile spasms have always been challenging to physicians who treat pediatric epilepsy. The condition has multiple etiologies, including hypoxic ischemic encephalopathy and tuberous sclerosis, and other inherited conditions. The AAN and the Child Neurology Society recently issued joint recommendations that include limited new information for the practitioner, although these recommendations currently are the only existing guidelines regarding treatment of infantile spasms. These guidelines conclude that adrenocorticotropic hormone offers effective treatment for infantile spasms but only for the short-term. Vigabatrin may be effective, based on existing clinical evidence. Pyridoxine is, of course, used extensively, although it is prescribed more widely in Japan and Europe than in the United States. Varying levels of clinical evidence exist regarding the effectiveness of nitrazepam, topiramate, and zonisamide in treating infantile spasms, with at least 2 studies reporting approximately 33% responsivity to zonisamide.

LENNOX-GASTAUT SYNDROME
Treatment of Lennox-Gastaut historically has been regarded as difficult, with monotherapy with valproate as the traditional approach. Felbamate was proven effective in a randomized placebo-controlled trial. The use of felbamate is limited by potential hepatic and bone marrow toxicities, such as aplastic anemia, but it remains a useful option in many cases. Topiramate and lamotrigine have become mainstays of therapy supported by strong clinical evidence of effectiveness. Zonisamide is also used, but it has not been tested in any well-constructed, randomized, controlled clinical trials.

Benzodiazepines occasionally are used as adjunctive agents. Phenytoin and carbamazepine may aggravate atypical absence seizures and atonic episodes in patients with this syndrome. Vagus nerve stimulation has potential benefit, demonstrating up to 88% resolution of atonic episodes after 6 months of treatment. The ketogenic diet is also helpful in some instances, and callosotomy is used as a therapeutic last resort.

CONCLUSIONS
The choice of an initial AED in the treatment of childhood epilepsy must begin with an accurate diagnosis of the involved seizure syndrome. An individualized assessment of risk factors and the consideration of comorbidities is essential to the optimization of therapy, and careful monitoring for treatment-emergent neurobehavioral consequences is an important part of initiating treatment of a child who is using an AED. Newer agents appear to offer equivalent efficacy and improved tolerability, as compared with older AEDs. Available options for treating children, especially those children with refractory conditions such as Lennox-Gastaut syndrome, have increased substantially. However, despite the progress made in recent years, epilepsy in many children remains refractory to therapy, and some children have difficulty tolerating available AEDs. This fact should provide a strong stimulus for the continuing development of new AEDs, especially those agents targeting the developing brain.

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REFERENCES


