



An Approach to Treating Idiopathic Generalized Epilepsy

With evidence-based recommendations relatively scarce, neurologists must rely on clinical judgment more often than not.

The last installment of *Epilepsy Essentials* (May 2008) focused on the topic of idiopathic generalized epilepsy syndromes. Typically beginning in childhood, adolescence, or early adulthood, these types of epilepsy manifest with a combination of seizure types. The most common generalized seizure types are absence, myoclonic, or generalized (from onset) tonic-clonic seizures (GTCs). In many instances, the name of the syndrome is derived from the age of onset and the primary seizure type that the person experiences. For instance, the syndrome of childhood absence epilepsy (CAE) describes childhood onset epilepsy, wherein the most common seizure type that the person experiences is absence. However, the child may have a combination of seizure types, including myoclonic and GTCs. In CAE, the myoclonic seizures and GTCS occur infrequently or rarely.

Because the idiopathic epilepsies are less common, and because some childhood syndromes may spontaneously remit,¹ there have been few studies that specifically address the effectiveness of treatment in idiopathic generalized epilepsy. In 2006, Dr. Glauser and colleagues performed a literature search in several medical databases, looking for trials that addressed monotherapy in either partial or generalized epilepsy syndromes. They looked for any article from 1940 to 2005. They identified 50 randomized controlled trials and seven meta-analyses. Of these, only four fit their criteria for Class I evidence, and two for Class II. The remainder was Class III. When stud-

ies that addressed generalized epilepsy were reviewed, they could make no recommendations about using antiepileptic drugs as monotherapy in generalized epilepsy. This was true both for adults and children.²

What We Think We Know

Monotherapy is effective in 80 to 90 percent of idiopathic generalized epilepsy syndromes.³ Often, the response occurs at relatively low doses of these medications. In short, only one medication may be needed, and at low doses in order to control this kind of epilepsy. However, there are few if any randomized double-blind controlled monotherapy trials for this kind of epilepsy. What should the neurologist do?

Valproate is considered the “first-line” choice of treatment for idiopathic generalized epilepsy. This information mainly is derived from large case series. In addition, there are case series that show its effectiveness for myoclonic seizures (for instance, in juvenile myoclonic epilepsy). However, there are several downsides to the use of valproate. Valproate is a hepatic enzyme inhibitor, and therefore has several important drug interactions (see *Epilepsy Essentials*, June 2007). Valproate is teratogenic, limiting its use in women in their childbearing years. It also may affect the liver, and caution must be exercised if the person has pre-existing liver problems. Finally, valproate can cause weight gain, and may need to be discontinued for this reason.

For the newer medicines, there are Class I and II studies which address specific generalized seizure types, though not

necessarily the specific epilepsy syndrome. For instance, there is good evidence that lamotrigine is effective for absence seizures, levetiracetam for myoclonic, and topiramate for generalized tonic-clonic seizures (Topamax is FDA approved for this purpose).⁴ Other broad spectrum agents, such as felbamate and zonisamide, have also been shown to be effective for certain types of generalized seizures. For the most part, the newer antiepileptic medications are less likely to interact with other medicines than the older agents. They also seem to cause fewer side effects. However, every medicine can cause side effects, and though less frequent with the newer agents, their use must be modified if side effects emerge during treatment.

Medical Devices

The vagus nerve stimulator (VNS) is a medical device that has been proven effective for the treatment of refractory partial epilepsy. Its usefulness in the generalized epilepsies has not been established with randomized clinical trials. One exception to this was the EO4 trial in the early 1990s. In contrast to other VNS trials, this trial included people with generalized epilepsy. When this group was separately analyzed, the effectiveness of the VNS for generalized seizures appeared to be the same as for partial seizures. In addition to this randomized study, there are many studies and case series which suggest that it is effective for idiopathic generalized epilepsy as well.⁵ Most physicians reserve this option for the idiopathic generalized epilepsies that do not respond well to medications.

Table 1. Overview of Treatment Options for Generalized Seizures

Seizure Type	Therapies That May Improve	Therapies That May Worsen
Absence	<ul style="list-style-type: none"> • ethosuximide, felbamate, lamotrigine, levetiracetam, topiramate, valproate, zonisamide • clobazam and acetazolamide may be effective as adjuncts • vagus nerve stimulation is less well studied, but may be effective in refractory idiopathic epilepsy syndromes 	carbamazepine, oxcarbazepine, phenytoin, vigabatrin, tiagabine
Myoclonic	<ul style="list-style-type: none"> • felbamate, lamotrigine, levetiracetam, topiramate, valproate, zonisamide • vagus nerve stimulation is less well studied, but may be effective in refractory idiopathic epilepsy syndromes 	carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, primidone
Generalized (from onset) Tonic-Clonic	<ul style="list-style-type: none"> • felbamate, lamotrigine, levetiracetam, topiramate, valproate, zonisamide • vagus nerve stimulation is less well studied, but may be effective in refractory idiopathic epilepsy syndromes 	

Worsening of Generalized Seizures

Certain medications, however, may worsen generalized seizures (see Table 1). Carbamazepine, phenytoin, vigabatrin, tiagabine have been reported to worsen absence seizures. Carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, primidone may worsen myoclonic seizures. Knowing this, the physician can select an optimal medication while simultaneously avoiding ones that could make the situation worse.

Conclusions

In practical use, the relative lack of evidence regarding the use of these medicines in idiopathic generalized epilepsy is a problem. Neurologists rely on evidence to make good clinical decisions. When solid evidence is lacking, the neurologist must make an inference. If the agent works for one kind of generalized seizure, perhaps it works for other types of generalized seizures as well. Neurologists will

need to continue in this way until more randomized trials for idiopathic generalized epilepsies are done. Ideally, these trials would also include a comparison of drugs, so that neurologists will be able to tell their patients confidently which medications are best. **PN**

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Conflicts of Interest Statement: Steven Karceski, MD: speaker for Cyberonics, Glaxo, UCB and Ortho-McNeil.

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