Gillette Children's Specialty Healthcare

A PEDIATRIC Perspective

March/April 2003 Volume 12, Number 2

New Treatment Options for PEDIATRIC EPILEPSY

by Beverly Smith Wical, M.D.

A child with epilepsy needs careful evaluation and management to receive the most appropriate and successful treatment. Treatment options for epilepsy have expanded significantly from just a few years ago. Thirteen anti-epileptic drugs (AEDs) are in general use, and the vagal nerve stimulator (VNS) therapy and ketogenic diet are also available for epilepsy control. In some cases, surgical procedures are used to treat epilepsy. This article, however, focuses on non-surgical epilepsy treatment options.

AEDs

When considering AEDs for use in young children, the patient's seizure type must be carefully evaluated. The medication chosen must be safe and effective for treating the specific type of seizure. Many of the new drugs can accomplish both goals. Minimizing potential side effects is also crucial when choosing AEDs.

It's unlikely a primary-care physician will need to become completely familiar with all of the AEDs available. However, becoming comfortable with the use of several agents for treating pediatric epilepsy is a reasonable and achievable goal.

By focusing on three of the newer anti-epileptic medications — topiramate (Topamax), oxcarbazepine (Trileptal) and levetiracetam (Keppra) — the primary-care provider can select appropriate options for the initial treatment of pediatric epilepsy. Oxcarbazepine and levetiracetam are among the newest AEDs in use in the United States. Topiramate has been in use since 1997. These three drugs successfully treat a broad spectrum of epilepsy seizure types with minimal side effects. If initial treatment with an AED is not successful in treating the seizure disorder, the patient should be referred to a pediatric epilepsy specialist for further evaluation and care.

Anti-Epileptic Medications

Topiramate deserves widespread consideration for treating pediatric epilepsy because it's effective for multiple seizure types. It's useful in treating partial seizures, primary generalized tonic clonic seizures, and in more difficult seizure situations, such as the Lennox-Gastaut syndrome.

The drug comes in 15- and 25-milligram (mg) sprinkle capsules, which are relatively easy to administer to children. It also comes in 25-, 100- and 200-mg tablets.

Side Effects of Topiramate
Side effects of topiramate include:
- Somnolence
- Slowed motor functioning
- Difficulty concentrating
- Anorexia/weight loss (in up to 10 percent of patients)
- Kidney stones (risk is approximately 0.5 percent)
- Acute myopia/secondary angle closure glaucoma (reported in about one in 800,000 children taking the drug)

Side effects of topiramate are usually mild at the lower doses. If the medication is started slowly and raised in small amounts, central nervous system side effects are significantly minimized.

Patients who develop redness of the eye or acute pain within the first month of treatment should stop the medication. Although the eye problem is very rare, it has been reported.

Oxcarbazepine is useful in treating partial seizures. It also has been used to treat generalized tonic clonic seizures. Although oxcarbazepine was released for use in the United States in January 2000, it has been used in Europe for years. Therefore, data exist concerning the drug's long-term effects.

Oxcarbazepine comes in a range of tablet sizes — 150 mg, 300 mg and 600 mg. These tablets are scored and can be broken in half. The drug also comes in a 300-mg/5 milliliters suspension. Typically, the dosage begins with 8 mg per kilogram (kg)/per day and then increases weekly by 10 mg/per kg/per day to a target of 30 mg/per kg/per day. The medication is given twice a day.

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Side Effects of Oxcarbazepine
Side effects of oxcarbazepine include:
- Sedation/somnolence
- Nausea
- Gastrointestinal upset
- Idiosyncratic skin rashes (skin rashes are seen less frequently with oxcarbazepine than with carbamazepine)
- Hyponatremia (deficiency of sodium in the blood)

An advantage to oxcarbazepine is that it comes in a liquid form that needs to be administered only twice a day.

Levetiracetam is useful for patients experiencing partial seizures. Although it's likely that its spectrum for clinical seizure control is actually much broader, that is still being delineated. Levetiracetam comes in 250-, 500- and 750-mg tablets, which are scored. Typically, treatment begins with 10 mg/per kg/per day. Doses are increased by 10 mg/kg/week until the target dose is reached. Maintenance doses are most often 20 to 40 mg/per kg/per day, and doses are given twice daily.

Side Effects of Levetiracetam
Side effects of levetiracetam include:
- Sedation/somnolence
- Mood or personality changes, including agitation, irritability and aggression

Again, beginning on the lower end of the dosing range and increasing, as tolerated, tends to limit these side effects.

Levetiracetam doesn't have any interactions with commonly used medications, which is an advantage for patients who take additional medications.

Refractory Epilepsy

When adequate seizure control hasn't been achieved despite a trial of three appropriate AEDs, the patient is considered to have refractory epilepsy. Several other factors help identify patients who may develop refractory epilepsy. They include:
- Multiple focal seizures prior to the onset of therapy
- Time between starting medication and obtaining seizure control
- Onset of seizures early in life

Often, a child with refractory epilepsy goes through a daunting series of medication changes. In many instances, this significantly improves seizure control. At other times, however, seizures persist despite careful management and appropriate use of AEDs. At that point, alternate ways of treating seizures are explored.

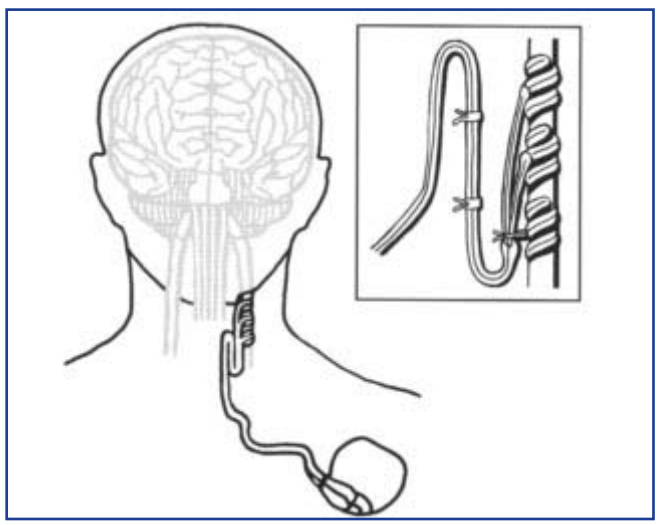
Other Treatments

Vagal Nerve Stimulator Therapy
A recent advance in therapy for refractory patients involves vagal nerve stimulation (VNS) therapy; the FDA approved this therapy five years ago. Originally known as the NeuroCybernetic prosthesis, the VNS therapy system is the first device approved to treat epilepsy. It has been implanted in approximately 16,000 patients.

A battery-operated generator is implanted below the skin on the left anterior chest wall. A neurosurgeon attaches electrodes from the device to the left vagus nerve (the VNS implantation does not involve surgery on the brain).

After implantation, the VNS generator is programmed by the physician to deliver an appropriate dose of electrical stimulation. The current is gradually increased, typically at one- to two-week intervals, until the target therapeutic dose is reached. There's also the possibility of providing additional stimulation (which can be self-administered or given by a caregiver) by placing — or swiping — a magnet over the chest where the generator is implanted. This magnetic activation of the VNS generator will stop or shorten a seizure in approximately 25 percent of patients who receive the implant.

VNS therapy can be effective against partial and generalized seizures, atonic seizures and tonic clonic seizures.



This diagram shows how the implanted VNS pulse generator, lower right, is linked by electrodes to the left vagus nerve in the neck. The enlarged section of the diagram (upper right) shows how the ends of the flexible silicone leads are wound around the nerve.

Illustration reprinted with permission from the Epilepsy Foundation®.

Side Effects of VNS Therapy
Side effects of VNS therapy may include:
- A change in voice quality during stimulation
- Hoarseness
- Cough or tickling in throat

Other side effects related to the surgical placement of the device may also occur.

Thus far, outcome data demonstrate that about one-third of patients experience major improvement in seizure control; one-third experience enough improvement that they feel it was beneficial to get the device; and one-third have no improvement in their seizures. VNS therapy typically doesn't provide immediate control; it can take weeks or months to see a response. A one-year trial of the device is reasonable for determining the level of benefit it will provide. To date, VNS effectiveness seems to continue over time.

Ketogenic Diet
Another strategy that may benefit children with refractory seizures is the ketogenic diet. Although this diet has been available for many years, it underwent a resurgence in use in the 1990s.

The diet is a rigidly controlled, high-fat, low-carbohydrate, calorie-restricted plan that alters the way the body obtains energy by forcing it to burn fat (or become ketotic). Although this diet has been used successfully for years, its success in controlling a number of very difficult seizure types isn't yet understood. The diet is useful for atonic, myoclonic and generalized seizures; it's less useful in controlling partial seizures.

Strict adherence to the diet — with careful medical monitoring and laboratory evaluations — is essential to maintaining health and growth while on the diet. Compliance can be a real issue, particularly in older children.

Side Effects of the Ketogenic Diet
Side effects of the ketogenic diet include:
- Metabolic consequences, such as hypoglycemia or hypocalcemia (vitamin and mineral supplements are always necessary for patients on the diet)
- Renal stones

The ketogenic diet should be managed only with a comprehensive team approach. A pediatric epilepsy specialist should work closely with a pediatric dietitian and other health-care team members.

Long-Term Outcome of Epilepsy
Up to 70 percent of patients will obtain adequate seizure control with their first AED. Long-term outcome data suggest that the eventual remission rate for generalized tonic clonic seizures is about 50 percent. In some patient groups, the remission rate may be as high as 80 percent. Long-term remission rates for focal epilepsy is much less, averaging around 25 percent.

For many patients, epilepsy is a lifelong condition. This makes it imperative to select the treatment that offers optimal seizure control with as few side effects as possible. Re-evaluation of therapy and potential side effects is needed on a regular and ongoing basis.

Author's Profile

Beverly Smith Wical, M.D.

Beverly Smith Wical, M.D., is a board-certified pediatric neurologist with special expertise in seizure disorders. She is medical director of Gillette's Infant and Toddler Program and has a special interest in the neurological conditions of young children. Wical began working with Gillette in February 1999. Prior to that, she was on the faculty of the University of Minnesota School of Medicine in the Division of Pediatric Neurology. She remains a clinical faculty member at the University of Minnesota.

A PEDIATRIC *Perspective*

Volume 12, Number 2
March/April 2003

A Pediatric Perspective focuses on specialized topics in pediatrics, orthopaedics, neurology and rehabilitation medicine.

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4-03SEXTON7600GG

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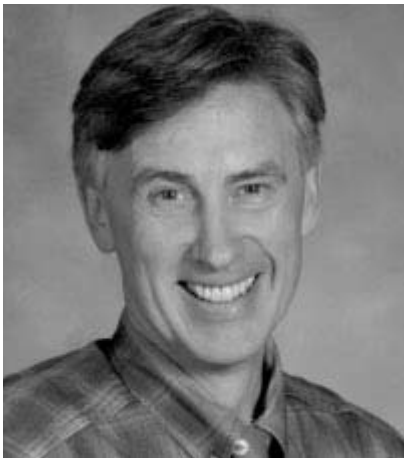
Gillette Welcomes John Day, M.D., Ph.D.



Gillette Children's Specialty Healthcare is pleased to announce the addition of John Day, M.D., Ph.D., to our medical staff. Day sees pediatric and adolescent patients with muscular dystrophy, spinal muscle atrophy and other neuromuscular conditions at our St. Paul clinic.

At the University of Minnesota, Day is a professor of neurology, director of the Muscular Dystrophy Center, medical director of the Muscular Dystrophy Clinic, and medical director of the Neuromuscular Biopsy Laboratory.

He received his medical degree from the University of Minnesota in 1977 and a doctorate degree in neurosciences from the Albert Einstein College of Medicine in New York in 1982. He completed training in internal medicine at Montefiore Hospital in New York and in neurology at the University of California-San Francisco, where he also completed a fellowship in clinical neurophysiology. Day has more than 15 years' experience treating pediatric neuromuscular disease.

To make referrals to Day at Gillette, call 651-229-3944. For more information on Gillette's Neuromuscular Program, call 651-229-1716.

Seizure Types/Symptoms

Generalized Seizures
Generalized Tonic Clonic Seizure (GTCS)
- Sudden onset
- Whole body involved
- Complete loss of consciousness
- Rhythmic jerking of whole body

Absence (Petit mal)
- Sudden onset, no warning
- Complete loss of consciousness
- Brief motionless stare
- Occurrence hundreds of times each day

Myoclonic
- Sudden onset
- Muscle jerking
- Brief, but may occur in clusters

Atonic (Akinetic)
- Generalized loss of tone and posture
- Brief

Tonic
- Generalized stiffening of the trunk and extremities, often with extension of the limbs
- May cause fall to the ground

Focal Seizures
Simple partial
- Consciousness is preserved

Complex partial
- Consciousness always impaired
- Motionless stare
- Duration is 30 seconds to 2 minutes
- May progress to GTCS

Partial with secondary generalization
- Focal seizure that spreads electrically until generalized tonic clonic activity occurs

(over)

Anti-Epileptic Drugs

These medications were all released for use in 1978 — or earlier — and have a longstanding history of clinical use in the United States.

AED	Treats Seizure Type(s)
Phenobarbital	Partial, GTCS
Phenytoin (Dilantin)	Partial, GTCS
Carbamazepine (Tegretol)	Partial
Divalproex Sodium/Valproic Acid (Depakote/Depakene)	GTCS, Absence, Myoclonic, Atonic, Partial

The 1990s marked a decade of advances in anti-epileptic drug therapy. The following drugs were released in 1993 and 1994:

AED	Treats Seizure Type(s)
Felbamate (Felbatol)	Partial, Atonic, GTCS
Gabapentin (Neurontin)	Partial
Lamotrigine (Lamictal)	Partial, GTCS, Lennox-Gastaut syndrome
Tiagabine (Gabitril)	Partial

These were released in 1997:

AED	Treats Seizure Type(s)
Topiramate (Topomax)	Partial, GTCS

In 2000, three medications were released for use in the United States:

AED	Treats Seizure Type(s)
Oxcarbazepine (Trileptal)	Partial, GTCS
Zonisamide (Zonegran)	Partial
Levetiracetam (Keppra)	Partial (and possibly others)