Advances in the Treatment of Epilepsy

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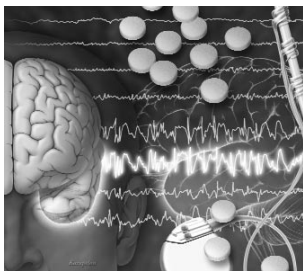
Significant advances have been made in the diagnosis and treatment of epilepsy over the past decade. With the advent of electroencephalographic video monitoring, physicians are now able to reliably differentiate epilepsy from other conditions that can mimic it, such as pseudoseizures. In addition, neuroimaging has changed the way treatment for difficult epilepsy is approached. As a result, the classification systems that have been in use since the early 1980s are currently being revised. A broader range of treatment options for epilepsy is now available. Many new antiepileptic drugs have become available in recent years, including felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide. These medications offer options for patients with epilepsy whose seizures cannot be controlled using the classic agents. Several classic antiepileptic drugs have been modified and reformulated. The ketogenic diet has resurfaced as a treatment option in certain types of epilepsy. The vagus nerve stimulator, approved in 1997, represents a completely new treatment modality for patients with seizures not controlled by medications. Epilepsy surgery is now a well-documented and effective treatment for some patients with intractable epilepsy. (Am Fam Physician 2001;64:91-8,105-6.)

A patient information handout on seizures and epilepsy, written by the authors of this article, is provided on page 105.



An estimated 1 to 2 percent of the U.S. population has epilepsy. In the past decade, more options have become available for patients with seizures. This article describes recent advances in the diagnosis and management of epilepsy.

New Concepts in Classification

EPILEPSY SYNDROME VS. SEIZURE TYPE

An understanding of the conceptual distinction between "seizure" and "epileptic syndrome" is essential. The word "seizure" refers to an abnormal behavior (with symptoms or signs) that results from abnormal discharges of cortical neurons. It is an observable phenomenon that is finite in time. By contrast, the term "epilepsy" refers to a chronic condition characterized by recurrent seizures. A syndrome is a cluster of symptoms and signs that occur together but, unlike a disease, a syndrome does not have a single known etiology or pathology. Thus, epilepsy (or epileptic syndrome), in contrast to a seizure, cannot be diagnosed simply by direct observation or video review because the diagnosis requires other information, such as age of onset, etiology, family history, seizure frequency, imaging studies, precipitating factors, electroencephalography (EEG) and natural history.

Most types of epilepsy are characterized by more than one type of seizure. Patients with focal (or partial) epilepsy may have simple partial, complex partial and secondarily generalized tonic-clonic seizures (e.g., partial seizures with secondary generalization). Patients with generalized epilepsy may have one or more of the following seizure types: absence, myoclonic, tonic, clonic, tonic-clonic and atonic. Thus, no seizure type is specific for a single type of epilepsy. Seizures are symptoms, and patients should be treated for a type of epilepsy, not for a type of seizure.[1] *Table 1* shows the main seizure types and their characteristics. *Table 2* shows the main types of epilepsy.

NEW SEIZURE CLASSIFICATION

The international classification of epileptic seizures (ICES)[2] that was published in 1981 is widely used by physi-

Routine EEGs are highly specific for the diagnosis of seizures but are positive in fewer than 50 percent of cases and, therefore, are not a sensitive diagnostic test.

cians as a diagnostic tool. Despite some advantages, the ICES has limitations, the most important of which is that it is based on clinical and EEG data.[2,3] An alternative seizure classification, the semiological classification, which is a purely symptom-based seizure classification, was recently proposed.[4] This simple classification consists of four major categories that correspond to symptoms affecting a different domain of behavior: sensorial (auras), consciousness, autonomic and motor. Because seizures can include symptoms in more than one domain of behavior, they are classified according to the predominant symptoms (without placing emphasis on particular symptoms as the ICES does). This classification can be made with the use of video recording but, because it is based exclusively on clinical data, it can be based on history alone.

The International League Against Epilepsy has recently acknowledged the shortcomings of the ICES system and is developing a new classification system.[5] The League's system will establish four levels of classification: (1) a descriptive seizure classification largely based on the semiologic classification described above; (2) a pathophysiologic seizure classification; (3) an epileptic syndrome disease classification comparable to the existing epilepsy classification[1,6]; and (4) a classification based on functional disability.

TABLE 1
Seizure Types and Characteristics

Seizure type	*Characteristics*
Generalized	
Grand mal	Unconsciousness, convulsions, muscle rigidity
Absence	Brief loss of consciousness
Myoclonic	Sporadic (isolated) jerking movements
Clonic	Repetitive, rhythmic jerking movements
Tonic	Muscle stiffness, rigidity
Atonic	Loss of muscle tone
Partial	
Simple (awareness is retained)	
Motor symptoms	Jerking, muscle rigidity, spasms, head-turning
Sensory symptoms	Unusual sensations affecting vision, hearing, smell, taste or touch
Autonomic symptoms	Stomach sensation
Psychologic symptoms	Memory or emotional disturbances (e.g., déjà vu, fear)
Complex (impairment of awareness)	Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, stereotyped movements
Partial seizure that becomes generalized seizure	Begins as partial (simple or complex) and evolves into grand mal seizure

DEFINITION OF STATUS EPILEPTICUS

In addition to changes in the classification of seizures, the definition of status epilepticus is evolving. While the classic definition required 30 minutes of convulsions, experts now agree that treatment protocol for status epilepticus should be initiated after five minutes of convulsive seizures.[7]

Diagnosis: Advances in EEG

ROUTINE EEG

Despite tremendous recent advances in neuroimaging, the EEG retains an important role in the diagnosis of epilepsy because seizures are a disorder of electrical function rather than of structure. Routine EEG may be useful in supporting a clinical diagnosis of epilepsy by showing epileptiform discharges (e.g., spikes or sharp waves) because it is highly specific. However, a routine EEG typically consisting of a 20- to 30-minute sample of brain activity is not highly sensitive. Fewer than 50 percent of routine EEGs are abnormal in patients who are known to have

epilepsy. While this yield increases with repeated EEGs, many patients with epilepsy continue to have normal EEGs.

EEG-VIDEO MONITORING

Prolonged EEG-video monitoring is critical in providing information about electrographic seizures and seizure semiology (video).[8] The prolonged nature of the recording allows a more thorough analysis of the EEG, thus increasing the likelihood of capturing epileptiform discharges. This analysis is also aided by the use of automated spike detection. More importantly, video monitoring allows recording of the actual events for which medical attention is sought.

For monitoring purposes, medications are carefully reduced to allow a seizure to occur within a reasonable time. Seizures can be detected by the patient or a family member and signaled by pressing an alarm, or they can be detected by an automated EEG seizure-detection mechanism. Careful correlation between clinical semiology (video) and ictal EEG allows for a definitive diagnosis of epilepsy or nonepileptic events. About 15 to 20 percent of patients referred for resistant seizures do not actually have epilepsy but instead have psychogenic seizures.

A definitive diagnosis of epilepsy can only be made using EEG-video monitoring.[9,10] The correlation between clinical semiology and ictal EEG also allows epilepsy to be categorized as partial or generalized and, in most cases, for the zone of seizure onset to be located.[8] These data are critical in deciding on the correct treatment options, including drug choice and surgical candidacy.

AMBULATORY EEG

Ambulatory EEG, analogous to the Holter monitor for cardiac arrhythmias, allows the recording of electrographic seizures but does not permit correlation between EEG and seizure semiology. Ambulatory EEG can be a useful extension of routine EEG,[11] especially in the differential diagnosis of seizures and nonepileptic events. It does not, however, replace comprehensive EEG-video monitoring.

INVASIVE EEG

Invasive EEG is necessary only when surgery is being considered and a regular (scalp) EEG evaluation fails to identify the zone of seizure onset with sufficient confidence, or when the zone of seizure onset must be defined with high precision in relation to nearby cortex. Various techniques, each having advantages and limitations, are available, including subdural, epidural, foramen ovale and intracerebral (depth) electrodes.[12]

Pharmacotherapy

Many new drugs for the treatment of epilepsy have become available in the past eight years.[13,14] The new drugs whose labeling has been approved in the United States are (in the order of their release since 1993): felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), levetiracetam (Keppra) and zonisamide (Zonegran). Each of these drugs was initially approved as adjunct treatment to a classic drug for refractory partial epilepsy. However, indications for these

TABLE 2
Comparison of the Main Types of Epilepsy

Generalized epilepsy—seizure types: absence, myoclonic, tonic, clonic, tonic-clonic and atonic
Idiopathic (genetic causes)
Childhood absence epilepsy, juvenile myoclonic epilepsy, epilepsy with grand-mal seizures on awakening, others
Symptomatic (cause known) or cryptogenic (cause unknown)
West syndrome, Lennox-Gastaut syndrome, others
Partial epilepsy—seizure types: simple partial, complex partial and secondarily generalized tonic-clonic seizures
Idiopathic (genetic causes)
Benign epilepsy of childhood with centrotemporal spikes ("Rolandic" epilepsy), others
Symptomatic (cause known) or cryptogenic (cause unknown)
Temporal lobe epilepsy, frontal lobe epilepsy, others

Psychogenic seizures can be diagnosed with certainty only by using EEG-video monitoring.

drugs are gradually broadening. For example, lamotrigine was recently labeled for monotherapy[15] and topiramate for treatment of primary generalized seizures.[16]

All of these drugs provide added seizure control and, in clinical trials on patients with highly refractory epilepsy, resulted in at least a 50 percent seizure reduction in 30 to 50 percent of patients. In clinical use in less selected populations, the efficacy of these drugs is even greater. They are also increasingly being used in settings other than epilepsy treatment, such as pain management and treatment of psychiatric disorders. Comparisons among these new drugs are difficult to make. In general, they are similar to each other in terms of efficacy. Therefore, the choice of a particular agent is often based on other factors, including side effect profile.

All anti-epilepsy drugs are central nervous system depressants and are associated with sedation, dizziness, ataxia, cognitive and visual disturbances, and gastrointestinal symptoms. These side effects are predictable, benign and dose- or rate-dependent. In most instances, the new antiepileptic drugs are better tolerated than the older drugs. However, significant differences exist among the drugs with regard to side effects, potential toxicity and pharmacokinetics.

Felbamate has a broad spectrum of activity in both partial and generalized seizures, but rare reports of fatal aplastic anemia and hepatic failure limit its use to patients for whom no other treatment alternative exists.

Gabapentin is characterized by excellent tolerability. It is not protein bound, has no appreciable hepatic metabolism and is excreted by the kidneys. Thus, gabapentin is appropriate for use in patients who require relatively quick titration, who have multiple drug intolerances or who are taking multiple drugs with the potential for interaction, including the elderly.

Lamotrigine has a broad spectrum of activity against multiple seizure types. Sedation is notably rare in monotherapy, and it even has an "alerting" response in some patients. One idiosyncratic side effect of lamotrigine, which is similar to effects of older antiepileptic drugs, is a rash. Infrequently (in less than 1 percent of adults), the rash can be serious and may progress to Stevens-Johnson syndrome, which can be life-threatening. Rashes are more common in children when lamotrigine is taken in association with valproate sodium (Depakote) and with rapid titration.

Topiramate also has a broad spectrum of activity. Weight loss has been noted, which can be a desirable lateral side effect. The development of nephrolithiasis, which is rare, and paresthesias, which is common, likely reflects carbonic anhydrase inhibition.

Tiagabine has no significant systemic or serious idiosyncratic adverse side effects, but it does have a relatively narrow spectrum of activity and must be titrated slowly. One limitation of lamotrigine, topiramate and tiagabine is that they need to be initiated at a low dosage and slowly increased in dosage over several weeks.

Levetiracetam is unique among the new antiepileptic drugs because it is effective starting with the initial dose. It also has a mechanism of action that appears to be different from that of other antiepileptic drugs and, like gabapentin, its tolerability and pharmacokinetics are very attractive. Levetiracetam is not metabolized by the liver (more than 60 percent is renally excreted unchanged), and less than 10 percent is protein bound. As a result, drug interactions are minimal.

Zonisamide has been used in Japan for 11 years and benefits from a large patient exposure, which supports its safety. *Table 3*[14] summarizes the principal characteristics of these new drugs.

In addition to the newer drugs, several chemical reformulations have been made to

the old antiepileptic drugs that have resulted in more favorable usability. Fosphenytoin (Cerebyx) is a reformulated version of phenytoin for use in the treatment of status epilepticus. Long-acting carbamazepine (Tegretol XR) allows for a twice-daily dosing that was not possible with the earlier version of carbamazepine. Oxcarbazepine (Trileptal) is a better-tolerated reformulation of carbamazepine. Intravenous valproate sodium (Depacon) can be useful for replacement in an acute setting or for rapid loading. Finally, rectal diazepam (Diastat) can be self-administered as a "fire extinguisher" by patients who have seizure clusters to abort impending status epilepticus.

In addition to fosphenytoin, other drugs are increasingly being used in the treatment of status epilepticus. In particular, midazolam (Versed) and propofol (Diprivan) may soon become standard therapy because of their

TABLE 3
Comparison of the Important Characteristics of New Antiepileptic Agents

Agent	*Unique side effects*	*Idiosyncratic reactions*	*Pharmacokinetics*	*Starting dosage/ average dosage*	*Titration/ administration*	*FDA indications*
Felbamate (Felbatol), 1993	Headache, insomnia	Aplastic anemia, hepatitis	Protein binding: 25 percent Metabolism: liver Liver enzyme: inhibitor	600 to 1,200 mg/2,400 to 3,600 mg	Slow (every week)/ two to three times daily	Focal and generalized epilepsy; adjunct and monotherapy
Gabapentin (Neurontin), 1993	Weight gain		Protein binding: 0 percent Metabolism: kidney Liver enzyme: none	300 mg/1,800 to 3,600 mg	Fast (increase every day)/three times daily	Focal epilepsy; adjunct
Lamotrigine (Lamictal), 1994		Rash	Protein binding: 55 percent Metabolism: liver Liver enzyme: inducer (mild)	25 to 50 mg/ 300 to 500 mg	Slow (every one to two weeks)/ twice daily	Focal epilepsy; adjunct and monotherapy
Topiramate (Topamax), 1996	Nephrolithiasis, paresthesias, weight loss		Protein binding: 15 percent Metabolism: kidney Liver enzyme: inducer (mild)	25 to 50 mg/ 200 to 400 mg	Slow (every one to two weeks)/ twice daily	Focal and generalized epilepsy; adjunct
Tiagabine (Gabitril), 1997			Protein binding: 95 percent Metabolism: liver Liver enzyme: inducer (mild)	4 mg/32 to 64 mg	Slow (every four weeks)/two to four times daily	Focal epilepsy; adjunct
Oxcarbazepine (Trileptal), 1999	Hyponatremia		Protein binding: 40 percent Metabolism: liver and kidney Liver enzyme: inducer (mild)	300 to 600 mg/ 600 to 2,400 mg	Slow (every week)/ twice daily	Focal epilepsy; adjunct and monotherapy
Levetiracetam (Keppra), 1999			Protein binding: 0 percent Metabolism: kidney Liver enzyme: none	1,000 mg/1,000 to 3,000 mg	Effective at starting dose/twice daily	Focal epilepsy; adjunct
Zonisamide (Zonegran), 2000	Nephrolithiasis, weight loss		Protein binding: 50 percent Metabolism: liver Liver enzyme: inducer (mild)	100 to 200 mg/ 400 to 600 mg	Slow (every one to two weeks)/every day to twice daily	Focal epilepsy; adjunct

NOTE: *New antiepileptic drugs are, overall, comparable in efficacy and have nonspecific dose-related side effects (e.g., fatigue, dizziness). The choice of a given medication depends largely on other factors, some of which are shown here.*

FDA = U.S. Food and Drug Administration.

Information from Tatum WO 4th, Galvez R, Benbadis S, Carrazana E. New antiepileptic drugs: into the new millennium. Arch Fam Med (In press).

very short half-life, which allows rapid titration based on the EEG.

Ketogenic Diet

The ketogenic diet was first advocated in 1921 after it was noted that ketosis and acidosis induced by a high fat-low carbohydrate diet had anticonvulsant effects similar to the effects of starvation. The treatment was rarely used once drugs became available to treat epilepsy. However, there has been a recent resurgence of interest in this treatment modality.

The diet is initiated with starvation until ketones are present in the urine. This therapy should be initiated in a hospital because of the risk of development of hypoglycemia. The diet consists of very large amounts of fat, 1 g per kg per day of protein and minimal amounts of carbohydrates. A typical fat-to-carbohydrate ratio is 4:1 or 3:1. A recent popular modification to the diet is the medium-chain triglyceride variant.

The diet is indicated for use primarily in young children with intractable symptomatic generalized epilepsy of the Lennox-Gastaut type, which is typically associated with diffuse brain abnormalities and some degree of mental retardation. Overall, 30 to 50 percent of children respond favorably. Those who respond show dramatic improvement, with at least a 50 percent reduction in seizure frequency within two to three weeks. The diet is typically maintained for two years. Some evidence suggests that it also may be effective in adults.[17]

While the ketogenic diet does not have the sedative and cognitive effects of antiepileptic drugs, there are some potential concerns regarding its effects on growth in children and on serum cholesterol levels in adults.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an entirely new treatment modality that has been extensively studied. VNS has an advantage over other electrical stimulations that have been investigated (e.g., cerebellar, thalamic) in that it does not require craniotomy. The mechanism of action is unclear, but it is likely mediated by the widespread afferent connections of the vagal nerve (which terminates in the nucleus of the solitary tract).

The NeuroCybernetic Prosthesis (Cyberonics, Inc., Houston) was labeled by the U.S. Food and Drug Administration in 1997 for adjunct treatment of partial epilepsy. It consists of two components: an electrode attached to the left vagus nerve through an incision in the neck and a generator, similar to a pacemaker, that is surgically implanted in the chest wall. Efficacy is comparable to adjunctive antiepileptic drugs (a mean seizure frequency reduction of 25 to 35 percent and a seizure frequency reduction of at least 50 percent in 40 percent of patients). Furthermore, efficacy may increase over time.[18]

Unlike medications, VNS has no significant neurocognitive or systemic toxicity. The only common side effect is hoarseness of the voice or a mild cough on stimulation. Experience with this new treatment modality is gradually increasing.[19] Like the newer antiepileptic drugs, VNS is being investigated for use in conditions other than epilepsy, and trials for its use in the treatment of depression are ongoing.

Epilepsy Surgery

A National Institute of Health consensus conference on epilepsy surgery estimated that

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seizures are intractable in approximately 20 percent of patients with epilepsy. Consequently, it is estimated that the number of surgeries performed is well below the number of possible surgeries,[20,21] despite the fact that surgery is now a well-accepted modality for the treatment of medically intractable epilepsy.

Medical intractability is a relative concept rather than an absolute one. The number of antiepileptic drugs that should be tried before a patient is deemed medically intractable is a matter of judgment. However, it is now well documented that when the first drug fails an adequate trial, the chances that another drug will succeed are less than 20 percent. If a second trial fails, the chances of future success with a medication are less than 10 percent.[22] In addition, because of all the new and forthcoming antiepileptic drugs, it is clear that trials of all antiepileptic drugs cannot be required before surgery is considered. Surgery should not be a treatment of last resort that is considered only after exhaustive and futile trials of every available antiepileptic drug. In practice, a usual medical trial may include two to four major drugs, with some used as monotherapy and at maximal tolerated dosages.

When considering surgery as a treatment for epilepsy, a patient's seizures must be frequent enough or severe enough to interfere significantly with quality of life. The risk-benefit analysis for surgery must be individualized, and the benefits must clearly outweigh the potential complications of the procedure. This analysis can be ascertained only through a comprehensive presurgical evaluation.[23,24] This evaluation is multidisciplinary and includes EEG-video monitoring,[8] structural imaging with special magnetic resonance imaging (MRI) using a dedicated epilepsy protocol,[25] and functional neuro-imaging.[26,27] Recent advances in imaging have significantly reduced the need for invasive EEG.

In general, postoperative seizure control is most successful in patients with temporal lobe epilepsy and has a greater than 90 percent rate of excellent outcome when MRI and EEG data are concordant.[28] Surgery for extratemporal epilepsy is often successful when associated with an identifiable structural lesion on imaging, but surgery in patients with nonlesional extratemporal epilepsy is less likely to result in elimination of seizures.[28]

Surgery is now a well-accepted treatment for intractable epilepsy.

Final Comment

Many new options exist for the treatment of epilepsy. Prolonged EEG-video monitoring is the first step in making an accurate diagnosis. If the first few drug trials fail (keeping in mind that "intractability declares itself early"), other treatment options should be investigated promptly.

In general, any patient who continues to have seizures despite treatment should be referred for further evaluation. If a patient's seizures occur once a week or more often, prolonged EEG-video monitoring may be a valuable method of determining if the patient has epilepsy, if the seizures are partial or generalized and from which cortical region(s) the partial seizures arise. This information will allow the physician to consider all the available treatment options to provide the patient with the best chance of gaining control of seizures. The respective places of various treatment modalities for intractable epilepsy are still evolving.[29]

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