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# The National Institute of Neurological Disorders and Stroke

of the

# National Institutes of Health

**Presents**

# Evolving Directions in the Management of Epilepsy:

## Epilepsy Diagnosis in the General Population

Jointly sponsored by the University of Cincinnati and SynerMed Communications

in cooperation with the American Epilepsy Society, American Academy of Neurology, and Epilepsy Foundation

This program is made possible by an educational grant provided by Ortho-McNeil Pharmaceutical, Inc.

May 2002

Dear Colleague:

Epilepsy presents a complex challenge to physicians, who must integrate the latest scientific and clinical knowledge with an individualized approach tailored to the specific needs of each patient. There is a growing recognition that the impact of epilepsy comes not only from the presence of seizures but also from the treatments themselves. Therefore, the approach to patients with epilepsy requires careful consideration in order to achieve an optimal balance of safety, efficacy, and quality of life.

We are pleased to present the second in a series of continuing medical education newsletters, *Evolving Directions in the Management of Epilepsy: Epilepsy Diagnosis in the General Population,* based on a conference presented by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NINDS/NIH). This newsletter uses four case studies to illustrate current approaches in epilepsy diagnosis and treatment among an adult population.

This newsletter is jointly sponsored by the University of Cincinnati School of Medicine and SynerMed Communications. It is supported by an unrestricted educational grant from Ortho-McNeil Pharmaceutical, Inc. We hope that you find it to be a useful educational resource for your practice, and that it well help you define the optimal strategies for improving the overall well-being of the many patients who suffer from this often difficult-to-treat disorder.

Sincerely,


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# EVOLVING DIRECTIONS IN THE MANAGEMENT OF EPILEPSY: EPILEPSY DIAGNOSIS IN THE GENERAL POPULATION

## Introduction

There is a growing recognition that the presence of seizures, the diagnosis of epilepsy, and the recommendations for patient management all have an impact on the lives of patients. Indeed, epilepsy presents a complex challenge to clinicians. It is a heterogeneous disorder that requires an accurate diagnosis and characterization of seizure type, careful selection of an antiepileptic drug (AED), and appropriate patient management. This case study newsletter is the second in a series of newsletters based on presentations from a March 2001 National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NINDS/NIH) conference, *Evolving Directions in the Management of Epilepsy.* Participating neurologists and epileptologists provided both etiology and epidemiology data, discussed current AED regimens and evaluated refinements that could improve their efficacy in the management of the disease, and also discussed special concerns in children, elderly patients, and women. Their views and conclusions are summarized in this newsletter.

This newsletter presents case studies that include current approaches in epilepsy diagnosis and treatment in the adult population. A follow-up newsletter will explore epilepsy management in pediatric and elderly patients. The cases included within this newsletter are as follows:

- A 35-year-old woman presented to the emergency department with her first tonic-clonic seizure. The importance of reaching an accurate diagnosis will be discussed, as well as AED selection, the likelihood of seizure recurrence, and quality-of-life issues.
- A 28-year-old man had two tonic-clonic seizures 6 years ago. He has been seizure-free on carbamazepine therapy. This case will address the withdrawal of AED therapy and the potential ramifications.
- A 27-year-old man has refractory complex partial seizures. Treatment considerations will be explored, including the option of epilepsy surgery.
- A 24-year-old woman with juvenile myoclonic epilepsy received valproate therapy. She is overweight and has experienced irregular menstrual cycles since age 12. This case will explore the clinical signs of reproductive health disturbances in women with epilepsy and the potential impact of AED treatment.

## Case 1: New-Onset Tonic-Clonic Seizures

This case describes a woman who experienced her first tonic-clonic seizure. As the patient is being evaluated, the primary consideration is to establish the type of seizure she has experienced: Was this a partial seizure that was secondarily generalized or was it generalized at onset? An early, accurate diagnosis of seizure type is essential for appropriate AED selection (see the "Single Seizure Checklist").

**LEARNING OBJECTIVES**

Upon completion of this activity, the clinician will be able to:

1. Discuss the importance of a careful history in the diagnosis of patients with epilepsy
2. Identify the benefits and drawbacks of therapy with older and newer antiepileptic drugs (AEDs) in terms of their efficacy, safety profiles, and drug interactions
3. Describe the decision-making process for withdrawing AED therapy
4. Select AEDs based on mechanistic profiles
5. Identify patients who are candidates for surgery
6. Discuss how the goals of therapy may be met in individual patients by matching overall therapeutic needs with the benefits of specific AEDs

### HISTORY

A 35-year-old woman presents to the emergency department with her first tonic-clonic seizure. There is no prior history of brain injury and no family history of epilepsy. She describes weekly episodes for the past several months of an unusual feeling described as butterflies in her abdomen with some nausea; the episodes last 30 to 60 seconds. Several of these episodes occurred during the morning of her first tonic-clonic seizure. She has no other relevant history, and review of systems was otherwise negative.

**Single Seizure Checklist**

- Was it a seizure?
- Was it really the first seizure?
- Are there risk factors for a second seizure?
  - Abnormal EEG?
  - Abnormal neurologic examination?
  - Abnormal MRI?
  - Sibling history?
- Should the person be allowed to drive?
- Should there be limitations on work?
- What are the risks of not treating?
- What are the risks of treating?

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Several features of this history can aid in determining whether the patient had a partial seizure that was secondarily generalized or a seizure that was generalized at onset. Abdominal sensations are the most common early symptoms of a partial seizure, especially those of mesial temporal lobe epilepsy.[1] In this case, the sensations probably represent simple partial seizures. Therefore, the brief duration, stereotyped sensation of butterflies in her abdomen with nausea is an important clue that indicates that her tonic-clonic seizure was secondarily generalized and also suggests that she has had more than one seizure prior to her emergency department visit. Often it is useful to interview family members or friends who have witnessed the patient's seizures; their information may aid in distinguishing one seizure type from another. A history of myoclonus points to a generalized-onset seizure. Frequently, patients fail to mention myoclonic jerks (thinking they are unrelated), and they should be questioned specifically about intermittent jerks of the extremities and shoulders.[2-4]

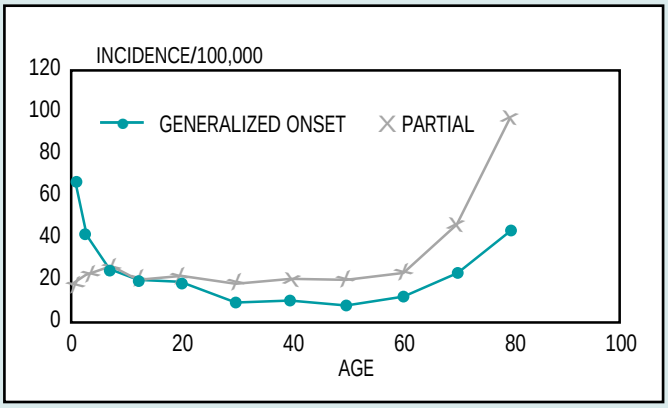
### EXAMINATION AND DIAGNOSTIC TESTS

The physical examination included a neurologic examination, electroencephalogram (EEG), and magnetic resonance imaging (MRI).

Although this patient had no additional relevant history, a complete patient history should seek the spectrum of risk factors for epilepsy in adults, including previous head trauma, central nervous system (CNS) infection, CNS malignancies, and occlusive cerebrovascular disease.[5] The most likely seizure type depends on age. The incidence of partial seizures is higher than generalized-onset seizures in the adult population (Figure 1).[6] A history of epilepsy, febrile convulsions, and/or head trauma can occur in patients with either generalized tonic-clonic (GTC) or complex partial seizures.[7] However, neonatal convulsions, cerebral palsy, and viral encephalitis are more common in patients with complex partial seizures.[8]

**FIGURE 1**

**AGE-SPECIFIC INCIDENCE OF PARTIAL-ONSET AND GENERALIZED-ONSET SEIZURES**

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Laboratory tests should include a complete blood count, tests of hepatic and renal function, and electrolytes. Metabolic or endocrine disorders may share clinical features with some complex partial seizures, but this occurs infrequently; therefore, tests for endocrine or metabolic disorders should be done only with justifiable suspicion. In the absence of an acute CNS syndrome such as prolonged confusion, fever, or other evidence for a rapidly progressive neurologic disorder, a lumbar puncture is not indicated. A screen for drugs of abuse should be performed in most cases. In this patient's case, there were no relevant physical findings, and there was no

indication of a metabolic disorder, acute syndrome associated with fever, or evidence for a rapidly progressive neurologic disorder. The drug screen also was negative. A pregnancy test is indicated because if the patient is pregnant, then the diagnostic and treatment plan may differ.

All adults with new-onset epilepsy should have appropriate neuroimaging studies. Although computed tomography (CT) with and without contrast, if already performed, may suffice in highly selected cases, most clinicians recommend an MRI. The MRI is a valuable diagnostic tool for evaluating patients with epilepsy. It is a noninvasive procedure that may help establish the etiology of the seizure disorder, the site of seizure onset, and whether a treatable lesion is the cause of seizure. In addition, in medication-resistant patients being evaluated for epilepsy surgery, the MRI is an essential component of the evaluation, selection, and operative strategy.

EEG findings also may be useful in distinguishing primary generalized versus secondarily GTC seizures.[9] Generalized interictal epileptiform discharges (IEDs) indicate generalized epilepsy; features of the generalized IEDs may suggest specific epileptic syndromes. On the other hand, focal IEDs generally indicate a partial seizure syndrome. It is important to note that the EEG in patients with complex partial seizures may be highly variable. For example, the interictal scalp EEG in temporal lobe epilepsies may show: no abnormality; slight or marked asymmetry of the background activity; or temporal spike sharp waves and/or slow waves, unilateral or bilateral, synchronous and/or asynchronous.[10] Continuous monitoring of the patient when awake and during all stages of sleep increases the yield of abnormal findings. In this case, the EEG recording did not show any abnormalities.

This patient's history as well as physical examination, laboratory tests, and neuroimaging studies indicate that she experienced a complex partial seizure that was secondarily generalized, rather than a primary GTC seizure.

### CLINICAL CONSIDERATIONS

*What is the risk that this patient will have recurrent seizures?*

Risk factors for seizure recurrence include seizure type, number of prior seizures, etiology, history of head trauma and intracranial infection, family history of epilepsy, abnormal neurologic examination, and EEG abnormalities.[11] For this particular patient, two factors—the seizure type and the likelihood that she has already experienced multiple seizures—are important.

Patients with partial seizures are more likely to have another seizure than those with generalized seizures. One study, which followed 208 patients for a mean duration of 4 years, demonstrated that seizures recurred in approximately 31% of patients; recurrence risks were estimated to be 14% by 1 year, 29% by 3 years, and 34% by 5 years.[12] Another study of 424 patients demonstrated risk of recurrence to be 36% by 1 year, 48% by 3 years, and 56% by 5 years.[13] Although this patient came to the emergency department with a first witnessed tonic-clonic seizure, her report of previous episodes of epigastric sensations indicates that she likely had previous partial seizures. Even with a normal MRI and normal EEG, the presence of previous partial seizures places her at a high risk (80%) for seizure recurrence.[14]

### TREATMENT

Most older and newer AEDs are effective for partial seizures. The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone were compared for the treatment of partial and secondarily GTC seizures in a double-blind, randomized study. This study demonstrated that carbamazepine and phenytoin were superior to phenobarbital and primidone.[15] A second study compared the safety and efficacy of valproate with carbamazepine for the treatment of complex partial and secondarily GTC seizures. Although carbamazepine and valproate were equally effective in controlling secondarily GTC seizures, carbamazepine was superior to valproate for complex partial seizures. Carbamazepine also was superior in terms of a composite score that reflected both control of seizures and adverse effects.[16] Therefore, among the older agents, carbamazepine and phenytoin are considered first-line treatment.

Among the newer AEDs, lamotrigine, oxcarbazepine, felbamate, gabapentin, and topiramate have been studied as monotherapy. Brodie et al compared lamotrigine and carbamazepine in newly diagnosed patients.[17] No differences in efficacy were found between treatments for seizure type (partial seizures with or without secondary generalization or primary GTC seizures). The proportion of patients who were seizure-free during the last 24 weeks of treatment was the same in both groups, although lamotrigine was better tolerated.[17] Lamotrigine and phenytoin monotherapy also have been compared in patients with newly diagnosed partial seizures or secondarily or primary GTC seizures. There were no significant differences between the two treatments in measures of efficacy. Although lamotrigine more frequently caused rash (which can rarely be serious and life-threatening), it was associated with a lower incidence of CNS side effects.[18]

**Clinical opinion: Carbamazepine or lamotrigine was considered by the conference participants to be the AED for this patient.**

Oxcarbazepine is a newly available AED that is chemically similar to carbamazepine but has a different metabolic pathway.[19] Its efficacy as monotherapy in adult patients with newly diagnosed epilepsy was established in two clinical trials. One trial compared oxcarbazepine with phenytoin; a second trial compared oxcarbazepine with valproate sodium.[20, 21] In both trials, the efficacy of the agents that were compared was similar.

The safety and efficacy of gabapentin as monotherapy were evaluated in three large, multicenter, double-blind, parallel-group, dose-controlled trials. There were no statistically significant differences among the three groups. Patients receiving carbamazepine had a higher withdrawal rate because of adverse events compared with the gabapentin 900-mg and 1800-mg groups. The results of these trials provide evidence that gabapentin is safe and efficacious as monotherapy for the treatment of partial-onset seizures.[22]

Felbamate was the first of the newer AEDs with indications for monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without generalization in adults. However, within 1 year after the introduction of felbamate in the United States, there were reports of aplastic anemia and 18 cases of liver failure, some fatal. In 1994, the Food and Drug Administration (FDA) advised clinicians to discontinue therapy in all patients except those who would suffer substantially from its withdrawal.[23]

Privitera et al compared topiramate with carbamazepine and valproate as monotherapy in newly diagnosed epilepsy.[24] Based on seizure type and profile, clinicians assigned patients to the carbamazepine or valproate arm. Patients were then randomized to receive the standard treatment, clinician's choice, or topiramate. This study demonstrated that topiramate as monotherapy was at least as effective and well tolerated as either carbamazepine or valproate.

Efficacy data for other newly available AEDs (tiagabine, vigabatrin, levetiracetam, and zonisamide) are less clear as these agents have demonstrated efficacy only in add-on, double-blind, placebo-controlled trials

in patients with refractory disease. Therefore, the decision whether to use such an agent in newly diagnosed epilepsy patients is more controversial. A recent study has shown, however, that the majority of newly diagnosed patients will derive similar treatment benefits with most AEDs, whether they are established or new.[25] By this measure, many of the newer AEDs offer significant advantages over older AEDs, including better safety profiles, efficacy in a broad spectrum of seizure types, and fewer drug interactions.[26]

**Clinical opinion: Participants in the conference agreed that they would consider monotherapy with newer AEDs based on safety, efficacy, and tolerability in individual patients.**

#### SPECIAL CONSIDERATIONS

*Endocrine side effects associated with long-term AED treatment*

Of particular concern in women are the endocrine side effects of AEDs. Several studies have explored the relationship between bone mineral density (BMD) and long-term treatment with AEDs. These studies support the hypothesis that AED therapy is an independent risk factor for reduced BMD in epileptic patients.[27,28] These studies also have demonstrated that adults receiving AED treatment are at higher risk of osteoporosis and should be offered bone densitometry.[28]

In monotherapy, the AEDs most commonly associated with altered bone metabolism are phenytoin, primidone, and phenobarbital. To date, there have been no reports of altered bone metabolism in patients receiving the newer AEDs (eg, topiramate, lamotrigine, vigabatrin, and gabapentin).[29]

*Interactions of AEDs with birth control pills*

A potentially important consideration in the selection of an AED in a woman in her childbearing years is the potential for interactions between some AEDs and birth control pills. AEDs that induce the hepatic cytochrome P450 system, such as phenytoin, phenobarbital, primidone, and carbamazepine, reduce the efficacy of oral contraceptives (OCs).[30,31] Oxcarbazepine and topiramate both induce OC metabolism, resulting in reduced OC efficacy.[32,33] Therefore, it may be necessary to alter the hormonal dose of the OC or to use AEDs that do not affect the metabolism of OCs.[34]

**Clinical opinion: AEDs that do not induce hepatic cytochrome P450 enzymes may be preferable in women during their childbearing years.**

*Quality-of-life issues*

Quality of life (QOL) in patients with epilepsy can be affected by seizures, side effects of medication, and psychosocial problems. Although clinicians tend to focus on management issues related to seizure control, it is increasingly recognized that an individual patient's social needs and concerns also must be addressed and met. In particular, issues and concerns for women of childbearing age with epilepsy include the ability to bear children; AED use during pregnancy; whether offspring will have epilepsy; the ability to safely raise a child; the ability to keep a job; and the ability to drive a car.

Independence and self-esteem also may be major concerns. Patient education regarding AED use, potential side effects, and drug-drug interactions is essential. Women who become pregnant must be made aware that stopping or reducing the dosage of their AED on their own may have harmful effects on the developing fetus.[35] Patient education tailored for women of childbearing age may alleviate unnecessary fears.[35]

## Case 2: Withdrawal of AED Therapy

This case describes a male patient with tonic-clonic seizures. He complains of adverse effects, including erectile dysfunction and CNS symptoms, and therefore would like to discuss stopping his AED therapy.

There are good reasons to consider withdrawal of AED treatment, such as remission, side effects, and QOL. Therefore, a decision to discontinue AED treatment is an individual one, made with a thorough understanding and careful assessment of the risks and benefits to the patient and with the individual patient's needs and preferences in mind.

#### HISTORY

A 28-year-old male had two tonic-clonic seizures occurring 2 weeks apart. These incidents occurred 6 years ago and were related to sleep deprivation while preparing for exams in college. He was readily controlled on the first AED that was prescribed—carbamazepine—and continues to take 600 mg/d. The patient complains of adverse effects, including erectile dysfunction and cognitive impairment. Since the beginning of treatment, his EEG and MRI results have been normal. At the present time, he is driving and working.

#### EXAMINATION AND DIAGNOSTIC TESTS

Although his EEG and MRI results have been normal since the initiation of AED therapy, it may be useful to try activation techniques to evoke behavioral or EEG manifestations of epileptic seizures. Certain types of activation, such as sleep deprivation, are particularly effective with specific seizure syndromes.[36]

**Clinical opinion: An EEG should be obtained following sleep deprivation in this patient, or an extended ambulatory EEG should be obtained in order to increase the yield for abnormal epileptiform discharges.**

In addition, the administration of an EEG before AED withdrawal serves as a baseline for comparison with EEGs that may be taken once AED therapy is discontinued.

It also would be useful to get a carbamazepine level in this patient before therapy is tapered. It has been demonstrated that seizure occurrence is related to serum concentrations of the AED.[37] Drug level determination not only will help guide the rate of tapering but also will reveal whether the patient currently is compliant with therapy.

#### CLINICAL CONSIDERATIONS

It is important to consider predictors of relapse before AED therapy is withdrawn. Predictors include age at onset of epilepsy, etiology, EEG pattern, type of seizure syndrome, severity of epilepsy, and the seizure-free interval.[38] A meta-analysis of 25 studies evaluated the association between risk of relapse and three commonly assessed clinical factors: age of onset, presence of an underlying neurologic condition, and an abnormal EEG (Table 1, page 6).

**TABLE 1**

**RELATIVE RISK OF SEIZURE RECURRENCE AFTER DISCONTINUATION OF AED THERAPY**

| | Relative risk (95% confidence interval) |
|---|---|
| Overall risk of seizure recurrence | |
| At 1 year | 0.25 (0.21 - 0.30) |
| At 2 years | 0.29 (0.24 - 0.34) |
| Age of onset of epilepsy (comparison to childhood onset) | |
| Adolescent onset | 1.79 (1.46 - 2.19) |
| Adult onset | 1.34 (1.00 - 1.81) |
| Remote symptomatic epilepsy (comparison to idiopathic epilepsy) | 1.55 (1.21 - 1.98) |
| Abnormal EEG | 1.45 (1.18 - 1.79) |

Adapted from Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology.* 1994;44(4):601-608.

This patient has many favorable predictors for successful withdrawal of AED therapy: adult age of onset, lack of an underlying neurologic condition, a normal EEG, few seizures, a short history of active epilepsy, seizure control with the first AED, and long seizure-free intervals.

In addition to these commonly assessed factors, the epileptic syndrome itself can be extremely useful for both assessing the prognosis for remission and predicting outcome following discontinuation of the AED.[39] Notably, outcomes after discontinuation have been poor in patients with juvenile myoclonic epilepsy (JME).[38] JME is an inherited disorder that occurs in approximately 5% to 10% of adults with epilepsy and is characterized by myoclonic jerks upon awaking, GTC seizures, and, less frequently, absence seizures.[40,41] In one 5-year study in patients with JME, absence seizures occurred in 33.3%, myoclonic jerks occurred in 97%, and GTC seizures occurred in 79% of patients. Ninety-three percent of patients had precipitating factors; sleep deprivation and fatigue were most common followed by photosensitivity, menstruation (for women), mental concentration, and stress. EEGs were frequently normal in treated patients.[40]

**Clinical opinion: The most important element in the diagnosis of JME is the patient's history; however, every attempt must be made to rule out JME in this case, because JME necessitates continued therapy.**

### TREATMENT

*How should therapy be discontinued?*

If this patient is an appropriate candidate for AED discontinuation, AED therapy should be withdrawn gradually. One study that evaluated the effects of carbamazepine withdrawal demonstrated that patients rapidly withdrawn over the course of 4 days experienced significantly more GTC seizures and GTC seizure clusters than did those whose therapy was withdrawn over the course of 10 days.[42] However, a comparison of a 6-week and 9-month period of AED withdrawal revealed no significant differences for the risk of seizure recurrence after discontinuation.[43]

**Clinical opinion: An appropriate tapering period for this patient would be 2 months.**

### SPECIAL CONSIDERATIONS

*How should this patient be counseled regarding driving?*

If JME is ruled out and if other factors indicate that this patient is a good candidate for AED discontinuation, and if he is tapered from his AED regimen without incident, his profile suggests he has a good chance of remaining seizure-free. However, the consequences associated with the potential for seizure recurrence can be fatal, especially for a person who is driving and working. Therefore, it is recommended that the patient not drive in the first 6 months after AED therapy is withdrawn. This is because the potential for relapse is greatest during this time.

**Clinical opinion: This patient should be counseled to refrain from driving for 6 months, the time during which relapse is most likely to occur.**

## Case 3: Refractory Seizures

This case describes a male patient who has suffered from complex partial seizures for the past 10 years and has failed several AEDs due to lack of efficacy or tolerability. Given the expanding therapeutic armamentarium for epilepsy, the physician should consider using one of several AEDs in this patient. Alternatively, the physician must consider whether this patient should be evaluated for surgery.

### HISTORY

A 27-year-old male had febrile seizures at age 2 and developed complex partial seizures at age 17. Seizures consisted of staring and chewing movements and alteration of consciousness lasting approximately 2 minutes. He was confused for approximately 5 to 8 minutes postictally. Seizure frequency is 3 to 4 per month on AED therapy. He is not driving, and he has lost his job because of his seizures. He had been treated with carbamazepine to maximally tolerated doses, which reduced seizure frequency to 2 to 3 per month. Phenytoin treatment reduced seizure frequency similarly, but it caused both drowsiness and gum hypertrophy. Valproate therapy failed: the patient experienced no change in seizure frequency and he gained weight. Lamotrigine reduced seizure frequency to 2 to 3 per month, but dizziness and diplopia occurred at the highest dose.

### EXAMINATION AND DIAGNOSTIC TESTS

His EEG showed left temporal spikes, and the most recent MRI, which was performed in 1990, was negative. Serum concentrations demonstrated compliance with carbamazepine, valproate, and lamotrigine.

### CLINICAL CONSIDERATIONS

*What does this patient's history and previous evaluations indicate about the site of origin of his seizures?*

This patient has a history of febrile seizures at age 2. Before the age of 5, between 2% and 4% of children in the United States will experience a convulsion during a febrile illness. Although approximately one third of these children will have further seizures with fever, only a small proportion

will develop unprovoked seizures later in life.[6] There is a known correlation between prolonged febrile seizures during childhood and later development of intractable temporal lobe epilepsy with mesial temporal sclerosis (MTS), which is the most common cause of complex partial seizures. However, it is exceedingly difficult to get a detailed history of febrile seizures that have occurred 25 years ago. While a history of prolonged febrile seizures (those lasting longer than 30 minutes) may give clues to the site of origin, no information was available as to the length of this patient's febrile seizures.

Other clues to seizure origin rest in his staring, chewing movements, and alterations of consciousness. Complex partial seizures with impaired consciousness, fixed stare, and oral-alimentary automatisms consisting of lip smacking, chewing, or swallowing are typical features of mesial temporal lobe seizures. Ictal recordings from patients with typical temporal lobe epilepsy usually exhibit 5- to 7-Hz rhythmic sharp spikes over the side of seizure origin.[44] Thus, this patient likely has temporal lobe epilepsy, most likely originating in the mesial temporal structures.

**TREATMENT**

*How do the known mechanisms of action of AEDs guide further selection of therapy?*

The known mechanisms of action of established and newer AEDs are provided in Table 2. Carbamazepine, phenytoin, valproate, and lamotrigine are known to act by limiting sustained repetitive firing through an action at voltage-sensitive Na+ channels.[45] Valproate also may act to block voltage-sensitive calcium channels and enhance GABA-mediated inhibition. Inhibition of both calcium and sodium channels is the presumed mechanism of lamotrigine.[45] Additional AEDs that were evaluated include topiramate, which has the largest number of known mechanisms of action, zonisamide, and levetiracetam. Another advantage of the newer AEDs is that some appear to have a broad spectrum of activity (Table 3). Topiramate is indicated for a broad range of seizure types (eg, partial seizures with and without secondary generalization and primary GTC seizures), and it also has received approval from the FDA for the

**TABLE 2**

**COMPARATIVE MECHANISTIC PROFILES AMONG SELECTED AEDs**

| Established AEDs | Na+ Channel Blockade | Ca++ Channel Blockade | Reduced Glutamate-Mediated Excitation | Enhancement of GABA Inhibition | Carbonic Anhydrase Inhibition |
|---|---|---|---|---|---|
| Phenytoin | + | | | | |
| Carbamazepine | + | | | | |
| Valproate | + | + (?) | | + (?) | |
| **Newer AEDs** | | | | | |
| Lamotrigine | + | + | | | |
| Topiramate | + | + | + | + | + |
| Zonisamide | + | + | | + | + |
| Levetiracetam* | | | | | |
| Oxcarbazepine | + | | | | |

*Mechanism of action of levetiracetam is currently not known.

Adapted with permission from White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. *Epilepsia.* 1999;40(suppl 5):S2-S10.

**TABLE 3**

**NEWER AEDS AND SPECTRUM OF ACTIVITY**

| | Partial | Lennox-Gastaut | Juvenile Myoclonic Epilepsy | Absence | Generalized Tonic-Clonic Seizures |
|---|---|---|---|---|---|
| Zonisamide | + | ?+ | ?+ | ?+ | ? |
| Gabapentin | + | - | - | - | ? |
| Lamotrigine | + | + | ?+ | ?+ | ? |
| Topiramate | + | + | ?+ | ? | + |
| Levetiracetam | + | ? | ?+ | ?+ | ? |
| Tiagabine | + | - | - | - | ? |
| Oxcarbazepine | + | - | - | - | ? |
| Felbamate | + | + | ? | ? | ? |

+ = randomized controlled trials
?+ = case reports or open-label trials only
? = no data
– = any negative data or evidence of worsening

Adapted with permission from Brodie MJ, French JA. Management of epilepsy in adolescents and adults. *Lancet.* 2000;356:323-329.

treatment of seizures associated with Lennox-Gastaut syndrome. Zonisamide has a relatively broad mechanistic profile and is effective against partial and secondarily generalized seizures, primary GTC seizures, generalized tonic seizures, and atypical absence seizures.[46] Levetiracetam is a new AED indicated as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Its mechanism of action is unknown.[47]

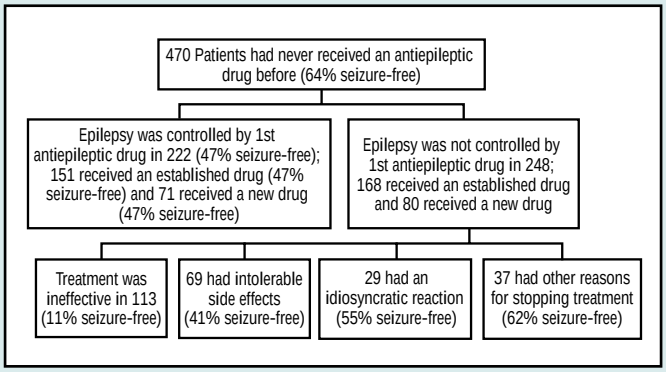
**Clinical opinion: In this patient, who has failed trials with AEDs that work via sodium and GABAergic mechanisms, a new AED that works via other additional mechanisms may provide improved therapeutic benefit.**

*Is this patient a candidate for surgery?*

Because of this patient's history of failed or incomplete response to AED therapy, his epilepsy could be considered refractory to treatment. The open-label, retrospective study by Kwan and Brodie suggested that most patients who have an inadequate response to initial AED therapy due to lack of efficacy are likely to have refractory epilepsy.[25] The outcome of medical treatment in 470 patients who had not received previous AED treatment demonstrated that epilepsy was controlled by the first agent in 47% of patients; 14% became seizure-free after treatment with the second or third AED; and in 3% of patients, epilepsy was controlled by two AEDs. In total, 64% of patients ultimately became seizure-free during AED therapy (Figure 2).[25]

**FIGURE 2**

**CONTROL OF EPILEPSY DURING MEDICAL TREATMENT IN 470 PREVIOUSLY UNTREATED PATIENTS**




Reprinted with permission from Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000;342(5):314-319.

In patients with refractory disease who have correctable structural abnormalities, some authors have argued that surgery should be considered as soon as treatment with two first-line AEDs has failed. A recently published randomized, controlled trial of surgery versus AED treatment in 80 patients with temporal lobe epilepsy found that surgery was significantly superior to prolonged medical treatment.[48] At 1-year follow-up, seizure-free rates were 58% in the surgically treated patients and 8% in patients who received continued medical treatment. The only death during the study period involved a patient randomized to continued medical treatment.

**Clinical opinion: Given the findings that suggest that surgery may be superior to AED therapy for patients with refractory temporal lobe epilepsy, the patient in this case would be a potential surgical candidate. A preoperative evaluation should be performed.**

**SPECIAL CONSIDERATIONS**

*How should this patient be evaluated for surgery?*

Presurgical evaluation includes extracranial ictal EEG and video monitoring. It is important to document with ictal video/EEG that the patient truly has medication-resistant epilepsy as many other disorders such as psychogenic nonepileptic seizures, panic disorders, sleep disorders, or convulsive syncope can present as epilepsy that is medication resistant. Most epilepsy surgery centers mandate neuropsychological testing and high-resolution brain MRI. Other useful tests that are performed by many centers and incorporated into surgical decision-making include ictal and interictal single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetoencephalography, and intracarotid amobarbital (Wada) test. Subtraction ictal SPECT coregistered with the MRI (SISCOM) allows subtraction of the interictal scans and coregistration with a structural MRI. In this case, the patient had a negative MRI in 1990; however, it is likely that the MRI protocol used at that time did not include the necessary imaging sequences and anatomic detail of the temporal lobes. The MRI with appropriate imaging requirements should be repeated. Oblique coronal images using T1-weighted and T2-weighted sequences with fluid-attenuated inversion recovery (FLAIR) are optimal in adult patients with partial epilepsy.[49]

If noninvasive tests are inconclusive or produce conflicting results about seizure localization, chronic intracranial ictal EEG recordings with depth, subdural, or a combination of electrode types may be needed.

Although certain elements of the presurgical evaluation are particularly important, a comprehensive evaluation should include a synthesis of evidence from diagnostic studies and other tests. At this point, the surgical team should determine the feasibility of surgery and its risks and benefits for the patient.

*What is this patient's prognosis after surgery?*

Once the preoperative evaluation is completed, a successful outcome versus the risks of complications following surgery should be considered. Many studies have evaluated the relationship between preoperative testing and postoperative outcome. Favorable prognostic indicators include an early age of seizure onset, mesial temporal lobe seizure onset, and pathologically identified MTS or foreign-tissue lesion. In this case, if repeated structural neuroimaging studies reveal MTS, the patient's surgical outcome may be favorable.

More than 80% to 90% of patients with mesial temporal lobe epilepsy may be seizure-free or nearly seizure-free following a total excision of the epileptogenic zone.[50] However, even seizure-free patients may require continued AED therapy, at least for a while.

## Case 4: Juvenile Myoclonic Epilepsy

This case describes a woman with a history of epilepsy. While her seizures are well controlled with valproate, she has menstrual irregularities and has inquired whether her midcycle spotting may be related to treatment. This patient's symptoms of reproductive dysfunction could be related to epilepsy, to her current AED (valproate), or both.

## HISTORY

A 24-year-old woman had her first GTC seizure at age 12, the morning after a slumber party. She experienced a second GTC seizure 6 months later when she had a flu and fever of approximately 102°F. She visited a neurologist after the second seizure; the neurologist empirically began carbamazepine treatment. Thereafter, she developed staring spells and had some morning jerks. The neurologist ordered an EEG, which exhibited generalized spike and slow wave discharges. She was diagnosed with idiopathic generalized epilepsy. She was started on valproate therapy and experienced no further seizures. As a result of seizure control, her school performance improved one full grade. (Although the diagnosis of idiopathic generalized epilepsy is correct, a more accurate diagnosis is JME. This is an important diagnosis because it directs therapy.) The patient has experienced irregular menstrual cycles since she was 12 years old, with the cycles ranging from 28 to 35 days. Once she began valproate therapy, her cycles became more irregular and prolonged, ranging in length from 35 to 45 days with some midcycle spotting.

## EXAMINATION AND DIAGNOSTIC TESTS

Upon measurement, the patient was 5 feet 3 inches tall and weighed 150 lb. Her body mass index (BMI) was 27 with a truncal distribution of obesity. She also had facial acne. An EEG taken at this time showed spike and slow wave discharges of 4 to 5 Hz that lasted no longer than 5 seconds. There was no clinical alteration during the discharges.

**Clinical opinion: As this patient's profile suggests reproductive dysfunction, an immediate change in her AED is required.**

## CLINICAL CONSIDERATIONS

Reproductive dysfunction is common in women with epilepsy and includes menstrual cycle disruption, anovulatory cycles, disturbances in hypothalamic and/or pituitary hormones, and disturbances in gonadal steroids. One third or more of women with epilepsy (WWE) may have abnormalities of ovarian function.[51] In one study, 35% of menstrual cycles in 17 women with temporal lobe epilepsy were anovulatory, compared with 8.3% of cycles in normal controls.[52] Another study of 50 women with temporal lobe epilepsy revealed that 28 had menstrual problems, 19 had reproductive endocrine disorders, and 10 had polycystic ovary syndrome (PCOS).[53] The number of WWE having features of PCOS (approximately 25%) is significantly higher than estimated frequencies in the general population, which range from 5% to 10%.[54,55] Although PCOS affects a higher proportion of WWE irrespective of which AED is used, it appears to be most likely to arise in women receiving valproate, which suggests that treatments other than valproate may be preferable.[56]

*How is the diagnosis related to treatment in this patient?*

As has been illustrated in the previous cases, a correct diagnosis of epileptic seizures is necessary to ensure proper AED therapy. Some AEDs (especially carbamazepine) that are typically used for partial-onset seizures may exacerbate primarily generalized seizures.[57] After carbamazepine therapy was initiated, this patient's EEG indicated that she had idiopathic epilepsy with generalized seizures. Therefore, carbamazepine was not the best choice for initial treatment as indicated by seizures that were controlled when valproate was initiated. Valproate is often used as first-line therapy for idiopathic epilepsy with generalized seizures.

*How should she be evaluated for possible reproductive dysfunction?*

This patient should be evaluated for possible PCOS. A diagnosis of PCOS has three requirements:

- An ovulatory disorder must be present. This can include cycle length >35 days or <8 cycles/year or anovulation with amenorrhea. A careful menstrual history is usually sufficient to make the diagnosis. Additional useful tests may include a midluteal progesterone level of <4 ng/mL, monophasic basal body temperature graphing, a negative result with an ovulation predictor kit, and an endometrial biopsy with proliferative endometrium.
- There must be evidence of androgen excess, which may be apparent from clinical manifestations such as hirsutism, acne, alopecia, acanthosis nigricans, or thorough laboratory testing, such as radioimmunoassay and DHEAS measurements.
- Other sources of anovulation must be ruled out, including an androgen-secreting tumor, hyperprolactinemia, hypothyroidism, or Cushing's syndrome.[58] It is important to note that obesity is found in approximately one half (range, 40% to 60%) of women with PCOS.[58]

## TREATMENT

*If the patient receives a diagnosis of PCOS, should the AED regimen be changed?*

Goals of AED therapy in patients with PCOS include: decreasing androgen levels; protecting the endometrium; avoiding the consequences of hyperinsulinemia; inducing ovulation in women who desire conception; decreasing cardiovascular risk; and attaining normal body weight. Weight loss is an important aim, for it has been shown to reduce hyperinsulinemia and hyperandrogenism and restore ovulatory function.[58] While dietary counseling and exercise are important steps, there are several good reasons for considering changing the AED. Although the patient's epilepsy is well controlled with valproate, use of valproate is associated with weight gain and gastrointestinal side effects.[59]

Other AED alternatives, such as topiramate and lamotrigine, are available. Trials of topiramate in epilepsy, migraine, and mood disorders found that weight loss was associated with its use.[60-62] It should be noted that among patients who take topiramate, weight loss typically occurs in overweight individuals; it is likely to be weight-neutral in other patient populations. However, a small percentage of patients may require topiramate discontinuation because of weight loss. In a study of women changed from valproate to lamotrigine, reproductive function improved significantly.[63] No drug has been subjected to a randomized clinical trial in JME, but topiramate was effective against primary GTC seizures, where a subset of patients were thought to have JME, and both lamotrigine and topiramate were effective against multiple seizure types in the Lennox-Gastaut syndrome.

*If the patient's obesity is the problem that causes her irregular menstrual cycle, should her medication be changed?*

If testing for PCOS is negative, it is possible that this patient's menstrual cycle irregularity may be related to her weight and truncal distribution of fat. The patient's BMI may place her in the category of overweight (see "The Body Mass Index", page 10).

Obesity is known to have negative effects on the reproductive system, depending on the amount and distribution of body fat. Epidemiologic studies suggest that being overweight can contribute to menstrual disorders and fertility problems. Central adiposity is particularly important in association with increased BMI. Weight loss has been shown to markedly improve menstrual cyclicity.[64] If an overweight patient is taking a medication associated with weight gain, it may be appropriate to prescribe a different AED, such as topiramate, that is associated with weight loss or a weight-neutral AED, such as lamotrigine.

### The Body Mass Index

The National Heart, Lung, and Blood Institute (NHLBI) has published obesity guidelines that propose the use of body mass index (BMI) to assess patients because the index is simple, correlates to fatness, and applies to both men and women. A BMI calculator can be found online at: www.nhlbisupport.com/bmi/. Classification of overweight and obesity by BMI is as follows:

| | Obesity Class | BMI (kg/m$^2$) |
|---|---|---|
| Underweight | | <18.5 |
| Normal | | 18.5 - 24.9 |
| Overweight | | 25.0 - 29.9 |
| Obesity | I | 30.0 - 34.9 |
| | II | 35.0 - 39.9 |
| Extreme Obesity | III | ≥ 40 |

Pi-Sunyer FX, Becker DM, Bouchard C, et al. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The Evidence Report . 1-258. 1998. NHLBI Obesity Education Initiative Task Force.

## Conclusion

The management of patients with epilepsy requires the integration of many factors. As highlighted by these case studies, an accurate diagnosis of seizure type is essential so that appropriate AED therapy decisions can be made. Second, expanding treatment options have enabled selection of AED therapy that can be better tailored to the patient. Newer AEDs allow physicians to choose treatments that have improved safety profiles, fewer drug interactions, and other benefits of treatment, such as weight loss, that may be an important overall therapeutic goal. Clinicians should strive to identify the epilepsy syndrome and match the AED. However, when the syndrome cannot be identified, using an AED with a broad spectrum of activity may be the optimal choice.

The ultimate goal is safe and effective AED therapy that positively impacts the lives of patients. In some patients with refractory disease, this goal may be reached by surgical treatment. In the vast majority, however, AED therapy provides the optimal balance of safety, efficacy, and QOL.

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# EVOLVING DIRECTIONS IN THE MANAGEMENT OF EPILEPSY: EPILEPSY DIAGNOSIS IN THE GENERAL POPULATION

## POST-TEST, PROGRAM EVALUATION, AND CME CREDIT REQUEST

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati College of Medicine and SynerMed Communications.

The University of Cincinnati College of Medicine designates this educational activity for a maximum of 1 hour in Category 1 credit towards the AMA Physician's Recognition Award (PRA). Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

To apply for Category 1 credit, you must:

- Complete the Post-Test and Evaluation Form
- Mail this form and a check in the amount of $5 to:
  UNIVERSITY OF CINCINNATI, OFFICE OF CME, PO Box 670567, Cincinnati, OH 45267-0567, Phone: (513) 558-7350, Fax: (513) 558-1708

Each participant achieving a grade of 70% or higher on the examination will receive documentation of CME credit hours earned. Participants receiving a grade of less than 70% on the exam will be notified and permitted to take one reexamination at no additional cost.

## POST-TEST

PLEASE CIRCLE THE CORRECT ANSWER.

1. Which of the following is not associated with partial-onset seizures?
   a. Generalized interictal epileptiform discharges
   b. Epigastric sensations
   c. An interictal EEG displaying temporal spike sharp waves
   d. A history of viral encephalitis

2. Which of the following is a potential benefit of many of the newer AEDs relative to older agents?
   a. Fewer drug interactions
   b. Broad spectrum of efficacy
   c. Improved safety profiles
   d. All of the above

3. Which of the following factors does not impact the risk of seizure recurrence in patients who are considered for withdrawal of AED therapy?
   a. Type of seizure syndrome
   b. Age at onset of epilepsy
   c. Previous failed attempt to discontinue therapy
   d. Period of time seizure-free

4. How do the known mechanisms of action of AEDs guide further selection of therapy?
   a. An agent with multiple mechanisms of action may be more effective than an agent with a single known mechanism of action
   b. Agents with complementary mechanisms may be combined for rational polypharmacy.
   c. Agents with unknown mechanisms may have fewer side effects when used as adjunctive therapy.
   d. a and b
   e. None of the above

5. Which of the following would not suggest that a patient is a candidate for surgery?
   a. Partial-onset epilepsy
   b. Failed or incomplete response to first AED
   c. Pathologically identified mesial temporal lobe sclerosis
   d. All of the above

6. In a woman with epilepsy who is overweight and has a diagnosis of polycystic ovary syndrome, how can treatment selection impact the overall goals of therapy?
   a. She should be continued on her therapy if it has controlled her seizures.
   b. Drug levels must be monitored to ensure that she receives an adequate AED dose.
   c. AEDs that are associated with weight loss should be considered for therapy.
   d. Although certain AEDs are associated with weight gain, obesity does not impact endocrine function.
   e. All of the above

## EVALUATION FORM

Expiration Date for Credit: May 2004

The University of Cincinnati College of Medicine would appreciate your comments regarding the quality of the information presented, and thanks you for your participation. Mail this form and a check or credit card information in the amount of $5 to: UNIVERSITY OF CINCINNATI, OFFICE OF CME, PO Box 670567, Cincinnati, OH 45267-0567, Phone: (513) 558-7350, Fax: (513) 558-1708.

| | Strongly Agree | Agree | Disagree | Strongly Disagree |
|---|---|---|---|---|
| 1. The program objectives were fully met. | a | b | c | d |
| 2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate. | a | b | c | d |
| 3. The educational activity has enhanced my professional effectiveness and improved my ability to: | | | | |
| A. Treat/manage patients | a | b | c | d |
| B. Communicate with patients | a | b | c | d |
| C. Manage my medical practice | a | b | c | d |
| 4. The information presented was without promotional or commercial bias. | a | b | c | d |
| 5. The program level was appropriate. | a | b | c | d |

6. Do you intend to change your clinical practice as a result of the information presented in this CME program? Yes No

Comments: _____

_____

7. How long did it take you to complete this activity?

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8. Suggestions regarding this material, or recommendations for future presentations:

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Deadline for receipt of the completed Post-Test/Self-Assessment and Program Evaluation is May 2004.