



A PHARMACY CONTINUING EDUCATION PROGRAM

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May 2005 "Seizure Disorders: Review of Therapeutic Options" 707-000-05-005-H01



**THIS MONTH**  
"Seizure  
Disorders"

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The goals of epileptic seizure therapy include an elimination or significant reduction in seizure frequency with a corresponding minimization of adverse effects associated with therapy. The focus of this lesson shall be the role of the newer AEDs This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

**The program ID # for this lesson is 707-000-05-005-H01.**

**Pharmacists completing this lesson by May 31, 2008 may receive full credit.**

**To obtain continuing education credit for this lesson**, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

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**The objectives of this lesson are such that upon completion the participant will be able to:**

1. Explain the classification of epileptic seizures.
2. List the goals of therapy for seizure disorders.
3. Summarize the available nonpharmacologic & pharmacologic options for treating seizures.
4. Describe the role of newer AEDs.
5. Discuss special considerations regarding therapy for special populations.
6. Evaluate appropriateness of monitoring.

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## OVERVIEW OF EPILEPSY

Epilepsy is a common, chronic, neurologic illness characterized by the recurrence of seizures. Worldwide, the prevalence of epilepsy ranges from 0.5% to 0.9%. In the United States, 2 million individuals have a diagnosis of epilepsy and 150,000 people are newly diagnosed annually. Incidence is highest among the very young (usually during the initial year of life) and the very old. For most patients, a diagnosis of epilepsy does not inhibit leading an independent and full life; however, approximately 30% of patients with epilepsy do have moderate to marked limitations on daily living.

There exists interpatient variability as to the specific etiology of the disorder. In general, seizures occur due to a disruption in the normal hemostasis of a neuron, which results in abnormal activity, and the possibility of subsequent seizure development. Various factors have been identified that may contribute to the occurrence of a seizure, including: genetic predisposition, mental retardation, cerebral palsy, head trauma, central nervous system infections, stroke, sleep deprivation, hormonal changes, medication intake, toxic antiepileptic drug (AED) concentrations, and small gestational age.

## EPILEPTIC SEIZURE CLASSIFICATION

Two major schemes for classifying seizure disorders have been developed by the International League Against Epilepsy (ILAE): the International Classification of Epileptic Seizures and the International Classification of Epilepsies and Epilepsy Syndromes. The International Classification of Epileptic Seizures categorized epileptic seizures through a combination of clinical description and electrophysiologic findings. The International Classification of Epilepsies and Epilepsy Syndromes is a more detailed classification scheme that takes into account other aspects of the disease such as age of onset, intellectual development, neurologic examination findings, and neuroimaging findings. Under the International Classification of Epileptic Seizures, there are two main categories: partial seizures and generalized seizures. Partial seizures are defined as initiating in a single hemisphere of the brain. Symptoms of partial seizures (i.e. motor function alterations, automatisms, or sensory or somatosensory symptoms) manifest asymmetrically unless the partial seizure develops into what is known as a secondarily generalized seizure. A partial seizure that occurs without an impairment of consciousness is referred to as a simple partial seizure. A complex partial seizure is one that involves an impairment of consciousness. Generalized seizures are described as involving abnormal neurologic activity in both hemispheres of the brain with bilateral motor symptoms and loss of consciousness. Generalized seizures may be further subdivided based upon electroencephalogram (EEG) measurements and clinical manifestations into absence, myoclonic, clonic, tonic, tonic-clonic, atonic, and infantile spasms. The International Classification of Epileptic Seizures also contains categories for "unclassified" seizures and status epilepticus. Discussion of these seizure disorder classifications is left for a future lesson.

## THERAPEUTIC OPTIONS

The goals of epileptic seizure therapy include an elimination or significant reduction in seizure frequency with a corresponding minimization of adverse effects associated with therapy. A key to directing therapy is establishing an accurate diagnosis that allows the specific seizure type to be determined. In order to accurately diagnose a specific seizure type, a detailed history of the seizure attack by both the patient and any potential witnesses is helpful. In addition, physical and neurological examinations, including an EEG and magnetic resonance imaging (MRI) of the brain, may be performed to aid in confirming the specific diagnosis. However, the results of an EEG are not always conclusive with regard to the establishment of a diagnosis of epilepsy. Approximately 15% of patients with a neurologic abnormality have repeatedly normal EEGs.

CE PRN® (ISSN 0199-5006) is owned and published by W-F Professional Associates, Inc.  
400 Lake Cook Road, Suite 207, Deerfield, Illinois 60015.  
William J. Feinberg, President

CE PRN® is published eleven times per year, monthly, January through November.  
Subscription rate is \$90.00 per year. Second-Class Postage paid at Deerfield, Illinois 60015  
and at additional mailing offices.

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May 2005

**NONPHARMACOLOGIC THERAPY**

Nonpharmacologic treatment options for epilepsy, including surgery, dietary changes, and vagal nerve stimulator implantation, are generally not first-line therapeutic options for the majority of patients. These are important options. Detailed discussions are left for future lessons. We shall concentrate upon drug therapy in this lesson.

**PHARMACOLOGIC THERAPY**

Clinical studies have demonstrated that the initiation of AED (antiepileptic drug) therapy after an initial seizure reduces the risk of recurrence. In one study, initiation of AED therapy after a single tonic-clonic seizure reduced the rate of recurrence from 51% to 25% over 2 years. When to initiate treatment in children or adults with seizures is still a contentious issue. Rarely would a child be initiated on AED therapy after a single seizure due to the potential for the development of cognitive and behavioral effects related to medications. The exceptions to this rule are children with risk factors (i.e. mental retardation) that result in an increased likelihood of seizure recurrence. These children are candidates for prophylactic treatment. In adults, therapy is more complex due to the psychosocial aspects of the disease such as limitations on work and normal activities like driving. Again, a single seizure does not automatically result in the initiation of AED therapy; however, if abnormal examination results, imaging, or EEG suggest a high probability of recurrence, a clinician may decide to prescribe an AED. When 2 seizures occur, treatment is probably indicated if the seizures were rather close in time, not separated over several years, and if the seizures resulted in an impairment of consciousness or the occurrence of deleterious effects such as falling or other injurious behavior.

There are a variety of factors that may increase the possibility of recurrence following a single seizure. Patients exhibiting these factors should be considered candidates for AED therapy. These factors include: an abnormal EEG, a known cause for the seizure such as a tumor or stroke, the occurrence of a generalized tonic-clonic seizure, or a high-risk occupation (i.e. driver or pilot).

Factors that lean against initiating AED treatment after a single unprovoked seizure include: a normal EEG, unknown cause of the seizure, the occurrence of a simple partial seizure, seizure activity during sleep, blood, liver, or kidney disease, or alcohol or drug-related seizures.

**ANTIEPILEPTIC DRUG THERAPY – MAKING A CHOICE**

Which antiepileptic medication to use as a first or second-line therapy in an individual patient depends on epilepsy type, drug-specific adverse effects, and patient preference. Few guidelines or treatment protocols have been published that give clinicians a strong consensus regarding the optimal AED for initial treatment of partial and generalized epilepsy. Differences with regard to treatment recommendations exist among the published literature. Table 1 summarizes first and second-line treatment choices for initial therapy of partial and generalized epilepsy from various references. These recommendations are merely a guide for clinicians.

**Table 1. First and second-line therapeutic options for initial treatment of partial and generalized epilepsy.\***

Reference	Seizure type	First-line therapy	Second-line therapy
Postgraduate Medicine 2002	Partial	Carbamazepine Oxcarbazepine Phenytoin	Felbamate Gabapentin Lamotrigine Levetiracetam Tiagabine Topiramate Valproic acid Zonisamide
	Absence	Ethosuximide Valproic acid	Lamotrigine Levetiracetam
	Idiopathic	Lamotrigine Valproic acid	Topiramate Zonisamide
	Symptomatic	Lamotrigine Topiramate Valproic acid Zonisamide	Barbiturates Benzodiazepines

Pharmacotherapy: pathophysiologic approach 2002	Partial	Carbamazepine Phenytoin Lamotrigine Valproic acid Oxcarbazepine	Gabapentin Topiramate Levetiracetam Zonisamide Tiagabine Primidone Phenobarbital Felbamate
	Absence	Valproic acid Ethosuximide	Lamotrigine
	Myoclonic	Valproic acid Clonazepam	Lamotrigine Topiramate Felbamate
	Tonic-clonic	Phenytoin Carbamazepine Valproic acid	Lamotrigine Topiramate Phenobarbital Primidone Oxcarbazepine
Disease of the Month	Partial	Carbamazepine Clonazepam Clorazepate Phenobarbital Phenytoin Primidone Valproic acid	Felbamate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate Zonisamide
	Absence	Ethosuximide Valproic acid	Lamotrigine Topiramate Zonisamide
	Atypical absence/atonic	Valproic acid	Lamotrigine Topiramate Zonisamide
	Myoclonic	Valproic acid	Lamotrigine Clonazepam Clorazepate
	Generalized tonic clonic/tonic/clonic	Carbamazepine Phenytoin Valproic acid	Felbamate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate Zonisamide

\*Noted references may limit the use of newer AEDs, that are discussed later in this lesson, to add on therapy in partial and generalized seizures.

Appropriate monotherapy with currently available AEDs results in the halting of seizure activity in up to 70% of diagnosed patients. If a patient does not respond favorably to initial monotherapy, the response rate falls dramatically, with only 16% of this subset of patients eventually becoming seizure free. Failure of a second AED reduces the chance of becoming seizure free even further. Patients receiving monotherapy should be titrated to the optimum dose prior to considering alternative monotherapy or add-on combination therapy.

After failure of monotherapy, the physician has a choice: to add on a new AED or to replace the current drug. Potential advantages of replacing current therapy include reducing drug toxicity by limiting exposure to multiple medications and being able to separately assess the efficacy of individual AEDs in a particular patient. By contrast, adding on a new AED could result in more rapid seizure control and higher seizure-freedom rates especially if a favorable drug-drug interaction exists between the combination AEDs. Very limited data are available that compare the outcomes of adding on or replacing AEDs in patients who have failed monotherapy. In one published study where the enrolling physician chose the drug and dosing strategy, patients were randomized to add on or replacement therapy after failure with initial monotherapy. The results of the study revealed no significant difference between the groups with regard to time to treatment failure or the cumulative number of patients seizure free for 12 months. The remission rates in both groups were approximately 15%.

### OTHER DRUG THERAPIES

Beyond the conventional AEDs, other medications have been used for patients with seizure disorders with some success. One of these medication classes is the benzodiazepines including clonazepam, diazepam, lorazepam, and midazolam. Intravenous formulations of lorazepam and midazolam are commonly used in the acute treatment of status epilepticus. Rectal diazepam gel (Diasat<sup>®</sup>) has been approved for acute repetitive seizures. Acetazolamide, a carbonic anhydrase inhibitor, has varying efficacy for numerous epileptic conditions including generalized tonic clonic, absence, and complex partial seizures. However, chronic use of this drug is not recommended due to the rapid emergence of tolerance. Clinicians have had some clinical success when administering acetazolamide intermittently to women who experience an increased seizure frequency during menses (i.e. catamenial epilepsy). Adrenocorticotropic hormone (ACTH) is often used for infantile spasms.

### WITHDRAWAL OF AED THERAPY

There is no consensus regarding the appropriate approach for withdrawal of AED therapy published in the biomedical literature. Relapse rates following withdrawal range from 12% to 63%. There are numerous risk factors that have been shown to be significantly associated with an unfavorable withdrawal from AED therapy. These include: age at onset of seizure disorder > 10 to 12 years, mental retardation, abnormal neurologic examinations, a family history of epilepsy, a poor initial response to AED therapy, use of > 1 drug at time of withdrawal, epileptiform EEG changes, slowing on EEG, emergence of EEG abnormalities during withdrawal, and juvenile myoclonic epilepsy.

Generally, patients that have an increased number of the above stated risk factors have a greater chance of experiencing seizure recurrence. Most clinicians would not recommend withdrawal of AED therapy prior to a 2-year seizure free period.

The approach for withdrawal of AED therapy differs between children and adults. In children, specific epilepsy syndromes have been identified that have a high probability of remission including: benign childhood epilepsy with centrotemporal spikes, childhood absence, and benign neonatal convulsions. Withdrawal of AED therapy should also be considered in children without these specific syndromes, but who do not have risk factors for relapse. In adults, no epilepsy syndromes with a high probability of remission have been identified; therefore, the choice to withdraw therapy is more complex. Studies that have evaluated success rates following AED withdrawal in adults have revealed a range of success from 34% to 77%.

Although a normal EEG is usually a positive sign, it does not guarantee success following AED withdrawal, particularly if a patient has numerous negative risk factors for relapse. On the other hand, an abnormal EEG can serve as compelling evidence against drug withdrawal, especially when a patient has other relapse risk factors. The tapering rate may or may not influence the clinical outcome following AED withdrawal. This is an area of contention. Tapering schedules vary from clinician to clinician, but generally a 6-month taper period is recommended. If a patient is currently receiving more than 1 medication, one drug should be withdrawn at a time.

### ROLE OF NEWER AGENTS

The focus of this lesson is the role of newer AEDs. These include felbamate, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and zonisamide. In 2004, the Therapeutic and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society reviewed the available clinical data of the new AEDs (excluding felbamate) for both new onset and refractory epilepsy. After an extensive review of the literature, the panel members made the following recommendations: gabapentin, lamotrigine, topiramate, and oxcarbazepine are efficacious as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders; lamotrigine is effective for newly diagnosed absence seizures in children; all of the newer AEDs are appropriate adjunctive treatment for refractory partial seizures in adults; gabapentin can be effective for the treatment of mixed seizure disorders; gabapentin, lamotrigine, oxcarbazepine, and topiramate are effective for the treatment of refractory partial seizures in children; limited evidence suggests that lamotrigine and topiramate are also effective for adjunctive treatment of idiopathic generalized epilepsy in adults and children, as well as treatment of Lennox-Gastaut syndrome.

#### Felbamate (Felbatol<sup>®</sup>)

Felbamate is the oldest of the "new" antiepileptics. Although its efficacy of felbamate has been documented for both partial and generalized seizures in combination with other drugs and as monotherapy for Lennox-Gastaut syndrome, this AED is a second-line agent due to the serious adverse effects associated with its use (i.e. aplastic anemia and hepatotoxicity). It is absorbed efficiently through the gastrointestinal system, is metabolized by the liver, and excreted into the urine. The target dose for monotherapy is 1800 to 4800 mg daily divided into 3 or 4 doses. For adjunctive therapy, the total daily dose is divided into 2 or 3 doses. Felbamate therapy should be initiated at a low dose and titrated up slowly at increments of 300 to 400 mg. The drug is an inhibitor of the cytochrome P450 (CYP450) enzyme system, and, therefore, inhibits the metabolism of phenytoin,

phenobarbital, valproic acid, and the carbamazepine metabolite, carbamazepine epoxide. A dosage adjustment may be needed when these medications are concurrently administered.

Overall, a total of 31 cases of aplastic anemia associated with felbamate use have been reported in the United States. Approximately 1 in 30,000 patients have experienced hepatic failure. Death due to felbamate-associated aplastic anemia and hepatic failure has been reported. Currently, the manufacturer recommends biweekly complete blood cell counts and hepatic function tests for the initial 6 months of therapy. Patients must also sign an informed consent form. Other reported adverse effects include nausea, headache, and insomnia.

### **Gabapentin (Neurontin®)**

Gabapentin is an AED structurally related to GABA, an inhibitory neurotransmitter. Although its exact mechanism of action is unknown, it is approved by the Food and Drug Administration (FDA) as adjunctive therapy for partial seizures and tonic-clonic seizures that initiate from a partial seizure (i.e. secondarily generalized seizures). Off-label, gabapentin has been prescribed for a variety of indications including trigeminal neuralgia and migraine. It is a water-soluble compound that is not metabolized by the liver. Renal excretion is the major route of elimination. The initial dose is 300 mg daily, and the target maintenance dosage is 900 to 3600 mg daily. However, patients may be titrated up to even higher doses. The titration can occur rapidly over 2 to 3 days, since it is fairly well tolerated. Since gabapentin is primarily eliminated through the kidneys, patients with renal impairment require lower dosages. No significant drug-drug interactions have been reported. Adverse effects may include sedation, dizziness, weight gain, movement disorders, and gastrointestinal upset.

### **Lamotrigine (Lamictal®)**

Lamotrigine has a broad spectrum of antiepileptic activity and is currently approved as adjunctive therapy for patients as young as 2 years of age, as monotherapy in adults, and for treatment of Lennox-Gastaut syndrome. It is effective for both partial and secondarily generalized tonic-clonic seizures. Lamotrigine is absorbed efficiently through the gastrointestinal system and is extensively metabolized by the liver. The half-life of lamotrigine is dependent upon its concurrent administration with medications that inhibit or induce its metabolism. Administration of lamotrigine with valproic acid (an enzyme inhibitor) results in a substantial increase in the half-life of lamotrigine: 25 hours to 59 hours. Concomitant administration with enzyme inducers, such as phenobarbital, phenytoin, and carbamazepine, results in a significant reduction in the half-life of lamotrigine: 25 hours to 15 hours.

Since lamotrigine is primarily given as an adjunctive agent, the initial dose varies dependent upon other AEDs a patient is receiving. Lamotrigine should generally be initiated at 50 mg daily in patients taking enzyme-inducing medications. The dose should be increased in increments of 50 mg at 2-week intervals, with a maintenance dose of 300 to 500 mg daily in 2 divided doses. For patients taking valproic acid, the initial dose of 25 mg every other day is increased by 25 mg increments every 2 weeks until a maintenance dosage of 100 to 200 mg daily is reached. The package insert for lamotrigine also contains detailed recommendations for conversion to lamotrigine monotherapy from more traditional AEDs. Commonly reported adverse events include diplopia, drowsiness, headache, and nausea. Most of these are dose related. A rash develops in 7% of patients taking lamotrigine, especially with concomitant use of valproic acid and rapid initiation of therapy. In some patients, this rash can be quite severe resulting in fever and lymphadenopathy. Patients should be counseled to contact their physician if a rash develops.

### **Levetiracetam (Keppra®)**

This AED is indicated for use as an adjunctive therapy for partial seizures in patients aged 16 years or older. It is rapidly and completely absorbed and is primarily excreted unchanged by the kidney. Treatment should be initiated at 500 mg daily in divided doses. The dose may be increased by 500 mg daily every 2 weeks, with a maximum recommended dosage of 3000 mg daily. It does not inhibit or induce the CYP450 enzyme system; therefore, drug interactions are minimal. Reported adverse effects with therapy include tiredness, anxiety, and moodiness. These effects may be due to an exacerbation of an underlying psychiatric disease such as depression.

### **Oxcarbazepine (Trileptal®)**

Oxcarbazepine is a prodrug that is immediately converted within the body to monohydroxy derivative (MHD), the active compound. It is approved for use as monotherapy or adjunctive therapy in the treatment of partial seizures in children older than 4 years of age and in adults. Oxcarbazepine has similar antiepileptic effects to carbamazepine; however, oxcarbazepine does not undergo autoinduction and it is not extensively metabolized by the CYP450 enzyme system. However, oxcarbazepine does induce CYP3A4 and inhibit CYP2C19. This inhibition can result in a reduced effectiveness of oral contraceptives and an increased serum concentration of phenytoin, respectively.

The initial dose of oxcarbazepine is 300 mg twice daily. This dose can be increased slowly at intervals of 300 mg per week to a maximum dose of 1200 mg daily. Reported adverse effects include hyponatremia, dizziness, and allergic skin reactions. Patients with an allergic-type reaction to carbamazepine may experience the same reaction with oxcarbazepine.

### **Tiagabine (Gabitril®)**

Tiagabine is FDA-approved as an adjunctive treatment of partial seizures in adults and children older than 12 years; however, use of the drug clinically is limited. The drug is metabolized in the liver via oxidation. Enzyme inducers, such as carbamazepine, phenytoin, and phenobarbital, increase the clearance of tiagabine by 60%. The initial dose is 4 mg daily, increased by 4 to 8 mg daily on a weekly basis until clinical response is achieved. The maximum daily dose of tiagabine is 56 mg/day. The drug is administered in 2 to 4 divided doses. Reported adverse effects include weight gain, behavioral abnormalities, and an increase in absence seizure exacerbations.

### **Topiramate (Topamax®)**

Topiramate is approved for use in partial seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome in children (> 2 years of age) and adults. Topiramate is also labeled for use in migraine prevention. Topiramate is eliminated principally by renal excretion. The liver metabolizes a small amount. The initial dosage of 25 to 50 mg daily is increased by 25 to 50 mg per week to a target maintenance dosage of 200 to 400 mg per day in two divided doses. In clinical studies, doses up to 1600 mg per day have been evaluated. There are minimal drug interactions involving topiramate; however, phenytoin and carbamazepine can accelerate the clearance of the drug. Dosage adjustments are needed when these medications are added on or discontinued from AED regimens that include topiramate. Reported adverse effects with therapy include dizziness, weight loss, somnolence, confusion, and, rarely, nephrolithiasis.

### **Zonisamide (Zonegran®)**

Zonisamide is approved as an adjunctive therapy for partial seizures in adults. Zonisamide is eliminated in the urine, and has no effect on the CYP450 enzyme system. Drug interactions with other AEDs have not been reported. Zonisamide is initiated at a dosage of 100 mg per day. The dose may be increased 100 mg at 2-week intervals, up to a maximum of 400 mg per day. Reported adverse effects with therapy include weight loss, drowsiness, rash, and the occurrence of calcium or urate kidney stones. Patients with a hypersensitivity to sulfonamides should not be administered zonisamide because it contains a sulfonamide component.

## **SPECIAL CONSIDERATIONS**

### **Female patients**

Due to the influences of hormones, such as estrogen and progesterone on neuronal function, female patients deserve special attention when evaluating therapeutic options for seizure disorders. Hormonal patterns change from menarche through pregnancy to menopause, and these changes may precipitate an increase in seizure occurrence. Oral contraceptive pills, which generally consist of estrogen and progesterone, do not routinely exacerbate seizure disorders; however, therapy with certain AEDs can reduce the effectiveness of oral contraceptives. Enzyme induction by AEDs including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone may result in a reduction in circulating estrogen and unbound progesterone. Women with seizure disorders who take the above mentioned AEDs with oral contraceptives are at an increased risk of contraceptive failure. These patients should be counseled regarding use of an additional contraceptive method while receiving concurrent therapy with an enzyme inducing AED.

Approximately 20,000 children annually are born in the U.S. to women with a diagnosis of epilepsy. Concerns arise during pregnancy due to the potential harm to both the woman and the neonate. Injury can occur due to unexpected seizures and the teratogenic potential of several AEDs. Therapy with a teratogenic AED should be avoided during pregnancy, if at all possible, as major (4% to 8% of children) and minor (6% to 20% of children) fetal malformations have been reported with their use. Reported effects of AEDs on the child include developmental delays, growth retardation, hypoplasia of the midface and fingers, higher rates of cognitive impairment, congenital heart disease, and neural tube defects. In order to prevent the occurrence of neural tube defects, folate supplementation is routinely recommended to pregnant women with epilepsy. A folate dose ranging from 0.4 to 5 mg daily is commonly administered in this situation even though administration of folate does not guarantee the absence of congenital defects.

### **Children and Elderly**

As stated prior, the very young and the very old remain the populations at highest risk for developing a seizure disorder. Children are at an increased risk of being diagnosed with catastrophic epilepsies such as infantile spasms (West syndrome), Lennox-Gastaut syndrome, and progressive myoclonic epilepsy. These epileptic syndromes do not occur frequently; however, treatment is extremely challenging, and multiple medications may be needed to provide a beneficial clinical effect. Children

may also be at an increased risk of cognitive adverse effects associated with AED use such as aggression, hyperactivity, memory impairment, and impairment of learning ability. Specific concerns exist among elderly patients with seizure disorders as well. The elderly may be at an increased risk of developing adverse cognitive effects with AED use. In addition, the elderly are often taking multiple medications for various disease states, so drug-drug or drug-disease interactions are more of a concern. Plus, the elderly generally have reduced renal and hepatic function, which can result in the modification of drug dosing regimens in this population.

### MONITORING

#### Drug concentrations

The goal of therapeutic drug monitoring in the epilepsy arena is to optimize outcomes through the appropriate use of serum concentrations. Although all AEDs have suggested therapeutic serum concentration ranges, no therapeutic range applies to all patients across the board. Some will respond to concentrations below the lower limit of a therapeutic range, while others will require concentrations above the range. Indeed, the optimum serum concentration for an individual patient may depend on a variety of factors including patient response to the AED and severity of the seizure disorder. Therapeutic drug monitoring should not replace clinical judgment when evaluating a patient's response to therapy.

### DRUG INTERACTIONS

Numerous drug-drug interactions exist both among the AEDs and between AEDs and other medications. A summary of various interactions between selected AEDs and other medications is presented in table 2.

Antiepileptic medication	Interacting drug	Outcome
Carbamazepine	Oral contraceptives	Decreased efficacy of oral contraceptives
	Doxycycline	Decreased levels of doxycycline
	Theophylline	Decreased levels of theophylline
	Warfarin	Decreased levels of warfarin
Oxcarbazepine	Oral contraceptives	Decreased efficacy of oral contraceptives
Phenobarbital	Oral contraceptives	Decreased efficacy of oral contraceptives
Phenytoin	Oral contraceptives	Decreased efficacy of oral contraceptives
	Folic acid	Decreased levels of folic acid
	Quinidine	Decreased levels of quinidine
Primidone	Chlorpromazine	Decreased levels of chlorpromazine
	Corticosteroids	Decreased levels of corticosteroids
	Tricyclic antidepressants	Decreased levels of tricyclic antidepressants
	Furosemide	Decreased renal sensitivity to furosemide
Topiramate	Oral contraceptives	Decreased efficacy of oral contraceptives

### CONCLUSION

Both nonpharmacologic and pharmacologic options are available for the treatment of seizure disorders. Nonpharmacologic options are generally reserved for patients who are refractory to therapy with an AED. Antiepileptic drugs remain the cornerstone of treatment. These include conventional medications such as carbamazepine, phenytoin, and valproic acid, as well as newer AEDs including lamotrigine, gabapentin, and topiramate. Special consideration should be given to female patients, children, and the elderly when developing a therapeutic plan for management of their epilepsy. Important components of therapeutic monitoring include appropriate use of serum concentrations and avoidance of drug-drug interactions.

### CASE

AL is a 25-year-old female who presents for an evaluation of recent onset seizure activity. She does not remember much of the attacks; however, her husband states that AL appears to lose consciousness and has no control of her motor abilities on both sides of her body. After a thorough physical examination, an EEG and a MRI of the brain is performed, the physician concludes that AL is suffering from new onset generalized tonic-clonic seizures. What would be an appropriate first-line therapeutic option for AL?

Since AL has new onset epilepsy, none of the nonpharmacologic options would be recommended at this point, as they are generally reserved for patients who are refractory. Reasonable first-line pharmacologic options for AL include carbamazepine, phenytoin, and valproic acid. The physician should begin therapy at the initial recommended dose and titrate AL to an optimal dose that controls her seizure frequency without intolerable adverse effects. Dependent upon which AED is chosen, AL should receive counseling regarding the potential for drug-drug interactions.

A few months later, AL returns. She has recently discovered that she is 2 months pregnant. What recommendations should be made to AL at this time?

If at all possible, AL should be removed from AED therapy or switched to another agent with a safer pregnancy profile. However, more than likely, AL will continue on AED therapy and therefore she should be supplemented with folic acid 0.4 to 5 mg daily.

### REFERENCES

The following references were found to be helpful in compiling this lesson. Participants may refer to these for further information.

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**LESSON EVALUATION**

Please fill-out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?
 

Explain classification of epileptic seizures	Yes	No	
List goals of therapy for seizure disorders	Yes	No	
Summarize nonpharmacologic & pharmacologic therapies	Yes	No	
Describe the role of newer AEDs	Yes	No	
Discuss special considerations for special populations		Yes	No
Evaluate appropriateness of monitoring	Yes	No	
2. Was the program independent & non-commercial?
 

Yes	No
Yes	No

	Poor			Average			Excellent	
4. Relevance of topic to your practice	1	2	3	4	5	6	7	
5. Author's ability to communicate	1	2	3	4	5	6	7	

6. What did you like most about this lesson? \_\_\_\_\_
7. What did you like least about this lesson? \_\_\_\_\_
8. How would you improve this lesson? \_\_\_\_\_
9. Further comments or suggestions for future programs \_\_\_\_\_

**(WATCH OUR WEBSITE FOR RESULTS OF PARTICIPANT EVALUATIONS)**

**Quiz—Please Select the Most Correct Answer**

1. Which of these newer AEDs has seen its clinical use limited due to adverse events?
  - A. Lamotrigine
  - B. Tiagabine
  - C. Felbamate
  - D. Topiramate
2. The goals of therapy for seizure disorders are best described as:
  - A. Elimination of seizures
  - B. Reduction in seizure frequency
  - C. Minimization of adverse effects
  - D. All of these
3. Which statement is FALSE regarding nonpharmacologic treatment options?
  - A. They are first-line options
  - B. They are generally used in refractory patients
  - C. They include ketogenic diet
  - D. They include surgical interventions
4. Factors that lean towards initiating AED treatment after a single unprovoked seizure include:
  - A. Abnormal EEG
  - B. Tumor-induced seizure
  - C. Occurrence of tonic-clonic seizure
  - D. All of these
5. A typical first-line AED choice for absence seizures is:
  - A. Lamotrigine
  - B. Topiramate
  - C. Valproic acid
  - D. Phenytoin
6. Which statement is TRUE regarding withdrawal of AEDs?
  - A. Approach to withdrawal of AED therapy differs between children & adults
  - B. Withdrawal of AEDs is commonly recommended in patients who have less than a 2-year seizure free period
  - C. A normal EEG is an indicator of guaranteed successful withdrawal
  - D. A 3-month tapering is recommended during withdrawal of AED therapy
7. Effective therapies for refractory partial seizures in children include gabapentin, lamotrigine, & oxcarbazepine.
  - A. True
  - B. False
8. Under the Internat'l Classification of Epileptic Seizures, categories of seizures are:
  - A. Partial & generalized
  - B. Partial & secondary generalized
  - C. Simple partial & complex partial
  - D. Unclassified & partial
9. Which of these newer AEDs has no significant drug-drug interactions?
  - A. Lamotrigine
  - B. Gabapentin
  - C. Oxcarbazepine
  - D. Topiramate
10. Females taking oral contraceptives do not need to be concerned with drug interactions involving their AED therapy.
  - A. True
  - B. False

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