Epilepsy: New Drug Therapies for the Pediatric Patient
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Upon completing this article, the pharmacist should be able to:
1. Discuss the mechanisms of action of the second generation antiepileptic drugs.
2. Compare and contrast the adverse effect profile of the second generation antiepileptic drugs.
3. Compare and contrast the pharmacokinetic and metabolic profiles of second generation antiepileptic drugs.
4. Discuss the drug interaction profiles of the second generation antiepileptic drugs.
5. Discuss drug treatment and withdrawal of drug treatment when considering antiepileptic drugs.
6. Describe the importance of a pharmacist’s interaction and counseling with the patient and their caregivers.

Introduction
Epilepsy is a chronic disorder characterized by a dysfunction in electrical brain activity causing recurrent unprovoked seizures. It can present due to a variety of etiologies, including infections, head trauma, and metabolic disorders as well as genetic abnormalities. Seizures types and severity can vary from patient to patient. The various types of seizures each have their own cause, whether it is known or not, clinical appearance, therapeutic management, and prognosis. Epilepsy syndromes are generally noted to be a complex array of signs and symptoms involving more than one seizure type. Certain seizure types have been found to be associated with specific epilepsy syndromes.

Epilepsy not only affects patients’ neurobiologic and cognitive functions, but also the psychological and social aspects of the patient, their families, and caregivers. Some patients are able to live relatively normal undisturbed lives and some patients are completely debilitated by their seizures.

In children, epilepsy not only affects the child, but the entire family and those associated with that child including teachers and friends. The support system of an epileptic patient plays a key role in the management of the patient’s disorder. Physicians rely on the caregivers and family members of the child to provide the information necessary to appropriately assess their neurologic disorder. The management of epilepsy in children is dependent on proper classification of the seizure type, making the family observations that much more essential.

In the last 15 years, a second generation of antiepileptic drugs (AED) has been approved and is now routinely being utilized in pediatric patients. As management of epilepsy continues to evolve with the introduction of new medications, it is important to understand the risks and benefits of these drugs.

Incidence and Epidemiology
Seizure disorders are the most common neurologic condition in children. They affect more than 4 percent of children and 1 percent of the adult population by age 20. Approximately 9 percent of the total population will experience a seizure, and about 2 percent to 4 percent will experience a recurrent seizure. Of the patients experiencing a first unpro-
voked seizure, epilepsy will occur in 1 percent. Worldwide, it is estimated that more than 10 million children under 15 have epilepsy.

An estimated 2.7 million Americans have been diagnosed with epilepsy. In the United States 25,000 to 40,000 children per year experience a first unprovoked seizure. About 30 percent of the 125,000 new cases of epilepsy diagnosed each year are in children less than 18 years old.

PROGNOSIS

The overall prognosis for children with epilepsy is favorable. Pharmacologically, the prognosis can be classified into four main groups. There are benign epilepsies, pharmacosensitive epilepsies, pharmacodependent epilepsies, and pharmacoresistant epilepsies. A positive indicator of long-term remission is an early response to drugs.

Patients may be well controlled yet still not be seizure free on AED therapy. There are also about 30 percent of patients who will be refractory to any drug therapy, and these patients may be eligible candidates for surgery. Other non-pharmacologic options to refractory epilepsy include vagal nerve stimulation devices and the ketogenic diet.

TREATMENT GOALS

The ultimate treatment goal of epilepsy is “no seizures, no side effects, and optimal quality of life.” Maintenance of the patient’s quality of life is significant in choosing AED therapy. More than 25 percent of adults and children with epilepsy experience treatment resistant seizures due to intolerable side effects. In the past, due to the negative side effect profiles of older AEDs, some patients have chosen to endure seizures rather than experience the side effects. The value of functioning in everyday life is worth more than being seizure free, yet debilitated in daily activities. First generation AEDs have a poorer side effect profile than the new generation of AEDs. The new generation of AEDs enable a balance between the side effects experienced and daily functionality. Much of the general algorithm that is followed in the treatment of an epileptic patient, assuming the diagnosis and seizure classification are correct, depends on finding a balance between the patient being seizure free, having the best quality of life possible with the diagnosis of epilepsy, and the ability of the patient to tolerate the side effects of the AED.

Comorbidities are a significant concern in treating patients with epilepsy. Antiepileptic drugs can interact with medications used to treat coexisting disease states. Both partial and generalized seizures types may have comorbidities including depression, psychiatric problems, disruptive mood disorders, anxiety disorders, thought disorders, and language disorders. Disease states associated with patients who have epilepsy include autism, cerebral palsy, mental retardation, and migraines. Attention deficit hyperactivity disorder (ADHD) affects 3 percent to 5 percent of children in the general population, but is twice as common in epilepsy patients. About 15 percent to 25 percent of people with cerebral palsy have epilepsy, and 15 percent of children with mental retardation have epilepsy.

Epilepsy treatment is dependent on classification and identification of the seizure type. Initial therapy and choice of AED is determined by the diagnosis. Although prognosis for epileptic patients is good overall, about 30 percent to 40 percent of patients will be refractory to treatment. AED choices are often determined by their dosing schedule, the age of the patient, insurance, and the patient’s compliance ability (Table 1). If a patient is unable to comply with their prescribed regimen, it may explain why they are having an increase in seizures compared to when they do.

Table 1. Considerations Prior to Treatment Initiation in Pediatric Patients

| 1. Proper diagnosis of seizure syndrome |
| 2. Assessment of child’s risk factors (individualized treatment) |
| 3. Comorbidities |
| 4. Age |
| 5. Adverse effect profile of AED |
| 6. Ease of medication administration (tablet vs. oral liquid) |
| 7. Time of titration (weeks vs. months) |
| 8. Attention behavior/psychomotor activity |
| 9. Seizure type/EEG findings |
| 10. Schedule/frequency of AED administration |
| 11. Compliance ability |
| 12. Insurance type |
comply. AEDs are considered ineffective in a patient only when the side effect profile of that AED becomes unacceptable, with the patient having continued seizures.

According to the American Academy of Neurology guidelines for the discontinuing of AEDs in seizure-free patients, physicians, patients, and patients’ families may consider discontinuing AED therapy only after assessing the risks and benefits to both the patient and society of a recurrent seizure if the patient has been seizure free for two to five years on AEDs, the patient has single type of partial seizure or single type of primary generalized tonic-clonic seizures, has a normal EEG with treatment, and has a normal neurologic exam or normal intelligence quotient (IQ).

**MONOTHERAPY VERSUS POLYTHERAPY**

Although not 100 percent effective, monotherapy is effective in about 50 percent to 70 percent of patients initiated on AED therapy. In those patients who are refractory to monotherapy, polytherapy is necessary. Patients are considered refractory when they fail two trials of monotherapy and one trial of a two drug therapy. Polytherapy is best used in refractory patients with the outcome goal of balancing side effects with a reduction in seizures.

The acceptance of monotherapy began in 1989 after a series of discussions between the Food and Drug Administration, the American Epilepsy Society, the National Institutes of Neurological Disorders and Stroke, and the pharmaceutical industries.

Advantages of monotherapy include association with fewer potential problems (toxicity, teratogenicity, and drug-drug interactions), generally being more cost effective, and ease of compliance to a single AED compared to schedules of multiple AEDs. Monotherapy for the initial first-line therapy of epilepsy has now become an accepted rationale for the treatment of epilepsy.

Some patients who have failed polytherapy actually show improved seizure control and fewer side effects with monotherapy. Recent evaluation of the effectiveness of polytherapy has shown little advantage for most patients. Polytherapy has an increased potential for drug-drug interactions, is associated with significant side effects, does not allow for individual drug efficacy, and may cause an exacerbation of seizures.

Use of a single drug at optimum tolerated serum concentrations produces excellent therapeutic results and minimal side effects in up to 80 percent of patients. The second AED only improved seizure control in an additional 10 percent to 20 percent of patients. According to one study, the failure rate of optimum monotherapy would be no higher than 17 percent.

**SECOND GENERATION AED THERAPIES**

Since 1994, seven new AEDs have been approved by the Food and Drug Administration (FDA). They have mechanisms of action that vary from those of the current AEDs. Having unique properties such as fewer side effects and drug-drug interactions than older AEDs means they may be more tolerable than the first generation AEDs. Current AEDs fall into one of three categories: those that augment inhibitory neurotransmitters, those that modulate excitatory neurotransmitters, and those that affect ion channels. \( \gamma \)-aminobutyric acid (GABA) is the inhibitory neurotransmitter which is increased in the mechanism of some AEDs. The excitatory neurotransmitters that some AEDs decrease are glutamate and aspartate. The AEDs targeting the ion channels target the sodium and calcium channels. Of the GABA affecting AEDs, some may target the GABA-A receptor and some target the GABA-B receptor.

The following antiepileptic drugs are discussed as follows: felbamate, gabapentin, lamotrigine, levetiracetam, tiagabine, vigabatrin, and zonisamide.

**FELBAMATE (FELBATOL\textsuperscript{®})**

**Mechanism of Action**

The exact mechanism of action of felbamate is unknown but may be similar to other AEDs. It may act as an antagonist of the glycine receptor site on the NMDA receptor by inhibiting the propagation of seizures.

**Pharmacokinetics**

Felbamate is highly and rapidly absorbed. Food and antacids do not affect the absorption of felbamate. Metabo-
The metabolism of felbamate occurs via hydroxylation and conjugation (about 50 percent) while the remainder is excreted unchanged in the urine. Pharmacokinetics of felbamate are linear. Dose should be decreased by 50 percent in renal failure.

**Side Effects**
Anorexia, weight loss, nausea, headache, and insomnia are some of the most frequently reported side effects of felbamate. In children, anorexia and weight loss may be most problematic. Aplastic anemia and acute liver failure have also been reported between two months to one year of use. These also appear to be limiting factors to the widespread use of felbamate. Aplastic anemia occurs in as many as one in 3,000, and hepatitis is seen in one in 10,000. It appears the highest risk is for women with a history of cytopenia, other AED allergies or toxicity, viral infections, or immunologic problems.

**Drug Interactions**
Along with the severe side effects associated with the use of felbamate, drug interactions also limit its use. By inhibiting the clearance of the following drugs, felbamate increases their serum concentrations: phenytoin, valproic acid, and phenobarbital. Phenytoin, carbamazepine, and valproic acid doses should be decreased by 20 percent to 30 percent when felbamate is added. Due to felbamate enzyme induction, carba-
mazepine serum levels will decrease and the metabolite 10,11-epoxide will increase if patients are concurrently on the two drugs. Felbamate also decreases the serum concentration of oral contraceptives.

**Place in Therapy**

Felbamate is not a first-line agent. The use of felbamate should be limited to patients not responsive to other AED therapy and whose epilepsy is severe enough that the benefits outweigh the risk of aplastic anemia and liver failure. Felbamate is indicated with the monotherapy and adjunctive therapy in patients with partial seizures with and without generalized seizures (for 14 and up); also indicated in children with partial and generalized seizures associated with Lennox-Gastaut Syndrome (patients age 2 through 14).

**Dose**

In children: dose to respond. Initial: 15 mg/kg/day titrate every two weeks by 15 mg/kg/day to a maximum of 45 mg/kg/day (3,600 mg maximum). Give dose three to four times daily.

**GABAPENTIN (NEURONTIN®)**

**Mechanism of Action**

Although gabapentin was designed to be a GABA agonist, it actually works by binding to an amino acid carrier protein and acts at a specific, but unknown receptor. It also may regulate some voltage-sensitive calcium channels.

**Pharmacokinetics**

Gabapentin displays dose-dependent bioavailability that varies among individuals. Food only slightly increases the rate and extent of gabapentin absorption. It is carried across the gut membranes by active transport via the L-amino acid carrier protein. The binding of gabapentin to this system also causes it to be saturable. The volume of distribution is high, with about 20 percent of plasma levels in cerebrospinal fluid, and up to 80 percent tissue concentrations in plasma levels. There is an age dependent volume of distribution and clearance rate. Both the volume of distribution and clearance rate in those from the ages of 4 to 6 is greater than that found in patients ages seven thru 12. Dialysis patients will see a 35 percent removal of gabapentin. Patients on hemodialysis should be given an initial dose and then redosed after every four hours of hemodialysis. The drug is excreted unchanged through the kidneys. Gabapentin must be given every eight hours due to its short half life of five to seven hours.

**Side Effects**

Peripheral edema, fatigue, somnolence, dizziness, and ataxia are common reported side effects followed by nystagmus, tremor, and diplopia. Some reports of aggressive behavior, such as hostility, emotional lability, and hyperkinesias have also been noted in children, prompting discontinuation of the drug. Gabapentin appears to have fewer CNS effects than do other anticonvulsants. Weight gain has been reported in children and adolescents on gabapentin therapy.

**Drug Interactions**

Patients on cimetidine have experienced a decrease in gabapentin levels by 10 percent. Gabapentin should not be taken with aluminum antacids due to a 20 percent decrease in gabapentin bioavailability. However, due to the fact that gabapentin does not inhibit or induce any liver system enzymes, major drug interactions do not occur.

**Place in Therapy**

Gabapentin is indicated for adjunctive for treatment of partial onset seizures with and without secondary generalization in patients 12 years and older. It is also indicated for adjunct treatment to control partial seizures in patients between the ages of 3 and 12.

**Dosing**

Dosing of gabapentin begins at bedtime on the first day and increased over the next three days. Gabapentin dosing regimens much higher than those recommended have been safely utilized in pediatric patients. Rapid titration also has been well tolerated unlike some of the AEDs that must be increased over a period of weeks.

Dosing in patients age 3 to 12 is initiated at 10 mg/kg/day to15 mg/kg/day, divided into three doses per day. Dose titration should occur over a three-day period. Usual dose for children age 3 to 4 is 40 mg/kg/day divided into
three doses per day. Maintenance dose for ages 5 through 12 is 25–35 mg/kg/day divided into three doses per day. Doses up to 50 mg/kg/day have been well tolerated.

**LAMOTRIGINE (LAMICTA®)**

**Mechanism of Action**

Multiple mechanisms of action exist for lamotrigine. Primarily, it acts by blocking the voltage and use dependent neuronal sodium channels. A dose-dependent inhibition of high voltage activation calcium currents is seen with lamotrigine. Lamotrigine also blocks the release of excitatory amino acid neurotransmitters such as glutamate and aspartate.

**Pharmacokinetics**

Lamotrigine has a bioavailability of 9 percent and is completely and rapidly absorbed. Food does not affect its absorption. Metabolism of lamotrigine occurs via UDP-glucuronosyl transferase extensively in the liver. Lamotrigine clearance is higher in children than in adults. Hemodialysis may remove up to 17 percent of a lamotrigine dose. The half life is altered in patients on dialysis. It becomes longer when not on hemodialysis and shorter during hemodialysis. During monotherapy the half life is about 24 hours and during polytherapy the half life is about 15 hours if the other AED is a hepatic enzyme inducer.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Frequency (divided doses)</th>
<th>Titration Increment</th>
<th>Usual Maintenance Range</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>15 mg/kg/day</td>
<td>TID-QID</td>
<td>15 mg/kg/day every 2 weeks</td>
<td>45 mg/kg/day</td>
<td>* dose to response 3,600 mg per day</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>3–12 years old: 10–15 mg/kg/day</td>
<td>TID</td>
<td>Over 3 days</td>
<td>3–4 years old: 40 mg/kg/day</td>
<td>5–12 years old: 25–35 mg/kg/day</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5–15 mg/kg/day</td>
<td></td>
<td>5–15 mg/kg/day</td>
<td></td>
<td>If also on VPA, max is 5 mg/kg/day</td>
</tr>
<tr>
<td>Levetriacetam</td>
<td>10–20 mg/kg/day</td>
<td>BID-TID</td>
<td>10–20 mg/kg/day every 1 to 2 weeks</td>
<td>40 to 60 mg/kg/day</td>
<td>100 mg/kg/day</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>4–16 years old: 8 to 10 mg/kg (maximum initial dose 600 mg/day)</td>
<td>BID</td>
<td>Every week over 2 weeks</td>
<td>20–30 mg/kg/day</td>
<td>50 mg/kg/day</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>0.1 mg/kg/day</td>
<td>BID</td>
<td>0.1 mg/kg/day every 1 to 2 weeks</td>
<td>Uninduced: 0.4–0.6 mg/kg/day</td>
<td>Induced: 0.7–1 mg/kg/day</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1–3 mg/kg/day</td>
<td>BID</td>
<td>1–3 mg/kg/day every 1 to 2 weeks</td>
<td>5–9 mg/kg/day</td>
<td>&lt; 5 years old: 15 mg/kg/day</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>25 mg/kg/day</td>
<td>BID</td>
<td>Titrated over 6 months</td>
<td>25–125 mg/kg/day</td>
<td>125 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Infants: 50 mg/kg/day</td>
<td>BID</td>
<td>Titrated every 3 days</td>
<td>25–125 mg/kg/day</td>
<td>150 mg/kg/day</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>1–2 mg/kg/day</td>
<td>BID</td>
<td>1–2 mg/kg/day every 1 to 2 weeks</td>
<td>4–8 mg/kg/day</td>
<td>12 mg/kg/day</td>
</tr>
</tbody>
</table>
Side Effects
Diplopia, drowsiness, ataxia, headaches, and rash are the most common side effects of lamotrigine. Adverse effects of lamotrigine may be pharmacodynamic in nature as they are seen more often in combination with other drugs. Lamotrigine may cause more adverse effects in children than in adults. Lamotrigine is not noted to cause weight gain.

A patient beginning lamotrigine therapy may develop a mild to moderate generalized, erythematous, morbilliform rash in the first three to four weeks of use that may necessitate the discontinuation of the medication. This rash is the most serious side effect of lamotrigine, occurring in about 0.8 percent of patients under age 16, and is seen more often in the younger children. However, some patients have reported a more severe Stevens-Johnson syndrome (SJS) type reaction. In order to minimize the rash, patients should be started on a low dose and escalated slowly over the course of a few weeks. The incidence of lamotrigine rash is increased with concurrent use of valproic acid, starting at a high dose, and rapid titration. The same type of rash is also possible with the use of carbamazepine, phenobarbital, and phenytoin. Toxic epidermal necrolysis (TEN) has been reported in a patient where the original SJS rash evolved to TEN. Eighty percent of TEN cases involve an anticonvulsant drug.

Dysguesia, or taste abnormalities, are also seen in carbamazepine, felbamate, and phenytoin. Dysguesia is possibly caused through the transmission of taste stimuli within the CNS. The mechanism by which dysguesia arises involves modification of the intracellular sodium, potassium, and calcium ion concentrations of the tongue receptors.

Drug Interactions
Lamotrigine, like gabapentin, does not inhibit or induce liver enzymes. Therefore, it too has a low drug interaction profile. The half life of lamotrigine is most often altered by other drugs such as carbamazepine, phenytoin, Phenobarbital, and primidone. Valproic acid substantially inhibits the clearance of lamotrigine by increasing the half life from about 22 hours to almost 45 hours. However, hepatic enzyme inducing medications decrease the half life from about 22 hours to only about 7.5 hours. Lamotrigine decreases valproic acid concentrations by about 25 percent. Lamotrigine does not interfere with the effects of oral contraceptives but, the oral contraceptive can reduce the lamotrigine serum concentration.

Place in Therapy
Lamotrigine is a broad spectrum anticonvulsant indicated for the adjunctive treatment of generalized seizures of Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures in patients 2 years old and older. It is indicated for monotherapy of partial seizures in patients who are converted from valproic acid or a single enzyme-inducing AED such as carbamazepine, phenytoin, or phenobarbital in patients 16 and older.

Dose
Lamotrigine is dosed from 5 mg/kg/day to 15 mg/kg/day. If the patient is also on valproic acid, then the maximum dose is 5 mg/kg/day.

LEVETIRACETAM (KEPPRA®)
Mechanism of Action
The mechanism of action of levetiracetam is unknown, but it may work through the inhibition of calcium dependent neurotransmitter release and GABA modulation. Reduction in high voltage activated calcium currents and delayed rectifier potassium currents as well as on GABA currents. Levetiracetam may also bind to a specific presynaptic binding site that modulates neurotransmitter release.

Pharmacokinetics
Levetiracetam is rapidly and completely absorbed following oral administration. Absorption is not affected by food, although it may delay the time to peak concentrations. Peak serum concentrations are reached within 0.5 to 1.3 hours. Metabolism is minimal via non-hepatic enzymatic hydrolysis but the majority is renally eliminated. Dose adjustments will be necessary in patients with decreased renal function. Dose adjustment is not necessary in patients with mild-to-moderate liver impairment, but severe hepatic cirrhosis should receive half of the usual dose. There have been a few case reports of levetiracetam being the main
culprit of a patient’s fulminant liver failure. Levetiracetam has linear pharmacokinetics. Clearance of levetiracetam is 40 percent higher in children than in adults with a relatively short half life at seven hours. An insignificant amount of drug is protein bound.

**Side Effects**

In one study, behavioral side effects occurred in 13.3 percent of patients receiving levetiracetam compared to placebo. Behavioral side effects in children include anxiety, aggression, and psychotic symptoms, but all are reversible by drug withdrawal or dose adjusting. No other severe systemic side effects have been noted. Central nervous system (CNS) adverse effects include sedation, fatigue, and coordination difficulties. Agitation, irritability, and depression have also been reported. To decrease the possibility of the side effects, the dose of levetiracetam should be escalated at a slower than normal rate.

**Drug Interactions**

Levetiracetam is not affected by hepatic enzyme inducing AEDs and does not affect the metabolism of other AEDs. Thus, levetiracetam has a good drug interaction profile. It is therefore useful in patients with hepatic impairment or who use multiple medications.

**Place in Therapy**

Trials in children show good efficacy and tolerability in refractory mixed seizure disorder. It is indicated for patients with partial seizures who have failed initial therapy and may be useful as monotherapy, but studies must be conducted. It is indicated as adjunct therapy for partial seizures in adults and off-label use in pediatrics is similar to the approved use in adults. Primary generalized epilepsy and, in rare situations, myoclonic epilepsy can be worsened by levetiracetam.

Levetiracetam is currently not approved for intravenous or oral loading dose. However, an observational study found that oral loading dose of the drug was tolerable in adults, with 11 percent of patients reporting only transient side effects. Therapeutic serum concentrations were reached about one hour after the loading dose was given.

**Dose**

The initial dose of levetiracetam is 10 mg/kg/day to 20 mg/kg/day with gradual titration every one to two weeks by 10 mg/kg/day to 20 mg/kg/day to a maintenance of 40 to 60 mg/kg/day. Levetiracetam doses as high as 100 mg/kg/day have been used safely. Compared to other AEDs, levetiracetam dose can be escalated relatively rapidly. It is normally dosed twice daily, however in high dose situations, the dosing frequency can be increased to three times a day to decrease the potential side effects.

**OXCARBAZEPINE (TRILEPTAL®)**

**Mechanism of Action**

The keto analog of carbamazepine is oxcarbazepine, a prodrug that converts rapidly to the active 10-monohydrate derivative (MHD) of carbamazepine. Unlike carbamazepine’s metabolite 10,11-epoxide, oxcarbazepine does not have an active toxic metabolite. It is thought to block the voltage-sensitive sodium channels, modulate the voltage activated calcium currents, and increase potassium conductance just as carbamazepine does. However, oxcarbazepine has different affinities to the channels than carbamazepine.

**Pharmacokinetics**

Oxcarbazepine is completely absorbed. It is metabolized extensively by non-inducible cytosolic ketoreductases to the active metabolite MHD. MHD is then inactivated by glucuronide conjugation and excreted by the kidneys. Children ages 2 to 5 may clear oxcarbazepine faster, and therefore may need larger doses to achieve the same serum concentration as adults. Oxcarbazepine has a short half life of two hours, but its metabolite has a half life of nine hours. Clearance is 40 percent higher in children ages 4 to 12 and 80 percent higher in children 2 to 4 when compared to adults.

**Side Effects**

Some of the more common side effects include dizziness, nausea, vomiting, headache, diarrhea, upper respiratory tract infections, constipation, dyspepsia, ataxia, and nervousness. CNS effects are most often seen with oxcarbazepine at higher doses (over 1,200 mg/day). Hyponatremia has been noted in up to 2.5 percent of patients on oxcarbazepine.
therapy. It is seen more often in elderly patients than in the younger patients. Hyponatremia may be worsened by the fact that patients may also be taking sodium-depleting drugs, such as diuretics. There is a cross reactivity between carbamazepine and oxcarbazepine structures. About 25 percent to 30 percent of patients who experience a rash with one will have a similar reaction with the other. Oxcarbazepine also has a warning for life-threatening dermatological reactions and multiorgan hypersensitivity.

Drug Interactions
Oxcarbazepine decreases the effectiveness of oral contraceptives by decreasing their bioavailability. It also increases phenytoin levels by about 40 percent due to CYP450 2C19 inhibition. Declines in lamotrigine levels are seen due to the induction of UGT isozymes. There is an increased clearance of the active metabolite MHD due to enzyme inducing drugs.

Place in Therapy
Oxcarbazepine is indicated for use in the United States as monotherapy (patients older than 4 years old) or adjunct therapy (patients under 2 years old) in treatment of partial seizures. Also, it is first line for primary generalized convulsive disorders. Oxcarbazepine may be effective in patients not responsive to carbamazepine. Patients with newly diagnosed partial epilepsy may be initiated on oxcarbazepine monotherapy.

Dosing
For children 4 to 16 years old, initial dosing is 8 to 10 mg/kg/day divided twice daily not to exceed 600 mg/day. Maintenance goal range for oxcarbazepine is 20 mg/kg/day to 30 mg/kg/day. Higher doses (up to 50 mg/kg/day) have been well tolerated. Dose titration should be weekly over two weeks. The typical maintenance dose in patients being converted from carbamazepine to oxcarbazepine is 1.5 times the carbamazepine dose for doses up to 1,500 mg/day; above 1,500 mg/day the ratio is 1:1 oxcarbazepine to carbamazepine. Patients between the ages of 2 and 3 may need to double the dose per body weight compared with adults and 4 through 12 year olds may need a dose 50 percent higher than adults.

TIAGABINE (GABITRIL®)
Mechanism of Action
Tiagabine is a potent and specific inhibitor of GABA uptake in the CNS. It is thought to enhance the action of GABA by decreasing its removal from the synaptic space. Tiagabine is the only GABA reuptake AED available.

Pharmacokinetics
Tiagabine is absorbed quickly and nearly completely after oral absorption. Tiagabine should be administered with food to avoid a rapid peak, which may cause CNS effects. Rapid dose escalation is also associated with CNS side effects. A linear relationship exists between daily doses and serum concentrations. Tiagabine is oxidized by CYP3A4 enzymes, therefore enzyme inducers increase its clearance. Tiagabine is eliminated faster in children than adults. Renal dysfunction does not change its pharmacokinetics. Patients with hepatic impairment have higher plasma concentrations of total and unbound drug and slower clearance. Clearance is 50 percent higher in pediatric patients than in adults. Tiagabine exhibits a diurnal effect where the trough concentrations are lower in the evening compared to the morning.

Side Effects
Common adverse effects are dizziness, asthenia, nervousness, tremor, diarrhea and depression. Side effects are usually mild to moderate in severity with most being dose related. CNS side effects can be minimized by taking tiagabine with food.

Drug Interactions
Enzyme inducers such as carbamazepine and phenytoin increase tiagabine clearance and decrease its half life. Tiagabine is displaced from protein by naproxen, salicylates, and valproate. However, tiagabine does not displace phenytoin, valproic acid, amitryptiline, tolbutamide, or warfarin.

Place in Therapy
Tiagabine is indicated for adjunct therapy in treatment of partial seizures in ages 12 and older.

Dosing
Dosing varies for induced and non-induced patients beginning with 0.1 mg/kg/day and increasing by 0.1 mg/kg/day
every two weeks to a maintenance dose of 0.4 mg/kg/day to 0.6 mg/kg/day. Induced patients have the same increments, but titrate up every one to two weeks with a higher end target dose of 0.7 mg/kg/day to 1 mg/kg/day. Maximum dose in 12 to 18 year olds is 32 mg/day while adults have a maximum dose of 56 mg/day.

**TOPIRAMATE (TOPAMAX®)**

**Mechanism of Action**
Topiramate is a sulfamate-substituted monosaccharide with multiple mechanisms of action. Topiramate is thought to act by blocking voltage-sensitive sodium and calcium channels, enhancing GABA activity, and antagonizing α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) subtype glutamate receptors.

**Pharmacokinetics**
Topiramate exhibits saturable binding to erythrocytes. Topiramate is excreted unchanged renally. Metabolism is increased by 50 percent when given with other enzyme-inducing AEDs. Inducers shorten the half life of topiramate. Topiramate exhibits age dependent clearance rate where clearance is higher by 150 percent in younger children versus older children, and higher in older children than adults by 50 percent. Its long half life of 10–23 hours allows for once to twice daily dosing.

**Side Effects**
Oligohydrosis and hyperthermias have been documented in children on topiramate in hot weather. Hypohidrosis and renal stones have also been reported. Ataxia, impaired concentration, memory difficulties, attentional deficits, confusion, dizziness, fatigue, paresthesias, somnolence, and “thinking abnormally” are all common side effects of topiramate. Word finding difficulties are unique to topiramate. However, most of these effects occurred during rapid dose escalation and at higher doses. There is an increased incidence of cognitive dysfunction in patients on dual therapy with topiramate and valproic acid. Impairment of language function and poor school performance have been noted, but both are reversible either by adjusting the dose or withdrawing the medication. Anorexia may lead to withdrawal of medication in small patients due to weight loss. Patients may also experience weight loss as a result of long-term treatment with topiramate. Somnolence contributes to cognitive dysfunction. There is also a risk of hyperchloremic nonanion gap metabolic acidosis, therefore patients should have their baseline and periodic serum bicarbonate levels checked.

**Drug Interactions**
Topiramate may have an inhibitory effect on the CYP2C19 system which may result in increased serum phenytoin concentrations. Both carbamazepine and phenytoin increase topiramate clearance. Slight reductions in digoxin, lithium, and amitryptiline levels may occur and slight increases in metformin levels may also be seen. Topiramate doses less than 200 mg/day are not likely to alter oral contraceptive pharmacokinetics. However, the drug does increase the clearance of ethynyl estradiol in a dose-dependent manner.

**Place in Therapy**
Topiramate is FDA approved in children older than 10 and in adults as initial monotherapy of primary generalized tonic-clonic seizures or partial onset seizures. It is also indicated as adjunct therapy in the treatment of primary generalized tonic-clonic seizures or partial onset seizures in pediatric patients age 2 and over and in adults. Topiramate is indicated in treatment of Lennox-Gastaut syndrome in patients over 2 and may be useful in infantile spasms.

**Dosing**
Children may need higher doses of topiramate to get the same concentration as adults. Cognitive and psychiatric side effects appear to be titration sensitive. Dosing in 2 to 16 year olds is initiated at 1 mg/kg/day to 3 mg/kg/day divided in two doses per day with weekly or biweekly dose escalation by 1 mg/kg/day to 3 mg/kg/day. The maximum dose is 5 mg/kg/day to 9 mg/kg/day dependent on the clinical outcome. Children under 5 have a maximum dose of 15 mg/kg/day and those over 5 have a maximum dose of 10 mg/kg/day above which they will have no further effect.

**VIGABATRIN (SABRIL®)**

**Mechanism of Action**
Vigabatrin irreversibly inhibits GABA transaminase, then converts it into a reactive intermediate that destroys the enzyme, thereby increasing GABA levels.
Pharmacokinetics
Vigabatrin has rapid absorption and is primarily renally excreted. Vigabatrin is not an enzyme inducer. The elimination half life in infants is about six hours. The time to peak concentration is 2.5 hours in infants and one hour in children and adults.

Side Effects
It is well tolerated with only mild adverse effects. The most common side effects are drowsiness, somnolence, fatigue, irritability, dizziness, headache, depression, confusion, poor concentration, nystagmus, abdominal pain, anorexia, rash, and weight gain. Behavioral abnormalities have led to withdrawal of the medication. Excessive weight gain is seen in children more often than adults. Psychosis, aggression, and exacerbation of seizures are also seen in children. Retinal toxicity, including irreversible constriction of visual fields, is seen in up to 40 percent of patients (both adults and children).

Drug Interactions
Vigabatrin has few drug interactions and does not interact with oral contraceptives. It does lower phenytoin levels by 20 percent to 30 percent, but this effect may not be seen until about four weeks of concurrent therapy.

Place in Therapy
Vigabatrin is indicated primarily for use in infantile spasms and refractory complex partial seizures not controlled by other therapies.

Dose
Initiate vigabatrin dose at 25 mg/kg/day to 75 mg/kg/day divided twice daily. Divide the dose into two daily doses. Titrate doses over six months to maintenance doses of 25 mg/kg/day to 125 mg/kg/day.

ZONISAMIDE (ZONEGRAN®)
Mechanism of Action
Zonisamide is a synthetic 1,2-benzisoxazole derivative classified as a sulfonamide. The mechanism of action is unknown, but believed to be related to reducing the repetitive neuronal firing via the blockade of voltage-sensitive sodium channels by reducing voltage-dependent T-type calcium channels, by facilitating dopaminergic and serotonergic neurotransmission, by weakly inhibiting carbonic anhydrase, and by blocking potassium induced glutamate release.

Pharmacokinetics
Zonisamide is absorbed completely, reaching a peak
concentration in two to six hours. It has a long half life of 60 to 80 hours in adults and is about 40 percent protein bound. Metabolism occurs via both CYP3A4 (50 percent) and N-acetylation (20 percent). About 30 percent to 35 percent of the drug is excreted unchanged renally. Distribution occurs to most tissues, but is twice as high in the kidneys, liver, red blood cells, and adrenal glands. Food decreases the rate, but not the extent of absorption of zonisamide.

**Side Effects**
Common side effects seen with zonisamide that are associated with a rapid dose escalation include somnolence, dizziness, anorexia, headache, nausea, agitation, and irritability. Patients hypersensitive to sulfa drugs may have reaction to zonisamide and thus should be used with great caution in confirmed sulfa allergy patient. There is a 2.6 percent incidence of kidney stones in patients treated with zonisamide. Oligohydrosis and modest weight loss have been reported as well as a case of hypohidrosis.

**Drug Interactions**
Hepatic enzyme inducers and CYP3A4 inhibitors can affect the concentration of zonisamide. Carbamazepine and phenytoin increase the clearance of zonisamide due to the CYP450 enzyme system effect. Phenobarbital may decrease the metabolism of zonisamide.

**Place in Therapy**
Zonisamide is approved as adjunctive treatment of adult partial onset seizures. Currently there is no approved indication for children under 16. However, zonisamide is sometimes used off label as treatment in intractable refractory seizures in pediatric patients.

**Dosing**
In children, dose should be initiated at 1–2 mg/kg/day and titrated every one to two weeks by 1–2 mg/kg/day up to 4–8 mg/kg/day up to max of 12 mg/kg/day. It is stable for 48 hours when mixed with water, apple juice, or pudding for patients who have trouble swallowing the oral solid dose formulation. Recently, an extemporaneous solution recipe has been published.  

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**Editor’s Note:** To obtain the complete list of references used in the article, contact Chris Linville at NCPA (703-838-2680) or at chris.linville@ncpanet.org.

**CONTINUING EDUCATION QUIZ**
Select the correct answer.

1. Epilepsy affects which of the following:
   a. Family, friends, and teachers of the epileptic patient
   b. The epileptic patient
   c. Neurobiologic and cognitive functions of the patient
   d. All of the above

2. What percent of newly diagnosed epilepsy cases in the United States are in children younger than 18 years old?
   a. 4%
   b. 9%
   c. 30%
   d. 35%

3. Therapeutically, prognosis of epilepsy can be classified into all of the following groups except:
   a. Pharmacosensitive
   b. Pharmacoresistant
   c. Benign
   d. Simple

4. Which of the following may cause hypohidrosis in children?
   a. Zonisamide
   b. Topiramate
   c. None of the above
   d. Both a and b

5. Common comorbidities of concern in epileptic patients include which of the following?
   a. Anxiety disorders, migraines, and diabetes
   b. Anxiety disorders, cerebral palsy, and autism
   c. Mental retardation, asthma, and cystic fibrosis
   d. Cystic fibrosis, psychiatric disorders, and asthma
6. The overall treatment goal of epilepsy can best be generalized as which of the following?
   a. “Few seizures, few side effects and minimal interruption to life”
   b. “Seizure freedom with minimal side effects”
   c. “No seizures, no side effects, and optimal quality of life”
   d. “No seizures, optimal quality of life, and monotherapy treatment”

7. Epilepsy treatment in children is dependent on all of the following factors except:
   a. Accurate diagnosis
   b. Patient age
   c. Time of day
   d. Risk factors

8. Patients are considered to be refractory to drug therapy when they
   a. Fail two trials of monotherapy and one trial of polytherapy
   b. Fail one trial of monotherapy and two trials of polytherapy
   c. Succeed with two trials of monotherapy and fail one trial of polytherapy
   d. Succeed with one trial of monotherapy and fail two trials of polytherapy

9. Which of the following AEDs weakly inhibits carbonic anhydrase?
   a. Gabapentin
   b. Topiramate
   c. Zonisamide
   d. Tiagabine

10. Hyponatremia is a side effect of which second generation AED?
    a. Neurontin®
    b. Sabril®
    c. Zonegran®
    d. Trileptal®

11. Which of the following medications is not displaced by tiagabine?
    a. Warfarin
    b. Naproxen
    c. Salicylates
    d. Valproic acid

12. A patient complains that he cannot seem to find the right words to say. The patient is on polytherapy of first and second generation AEDs. Which of the following medications is most likely the causal agent for the patient’s complaint?
    a. Phenytoin
    b. Lithium
    c. Topiramate
    d. Metformin

13. Monotherapy is effective in what percentage of patients on AED therapy?
    a. 40%–60%
    b. 50%–70%
    c. 75%–80%
    d. 85%–90%

14. The most serious side effect which may necessitate the discontinuation of lamotrigine is which of the following?
    a. Headache
    b. Rash
    c. Ataxia
    d. Drowsiness

15. A patient currently on phenytoin with uncontrolled epilepsy is having felbamate therapy added to their daily antiepileptic therapy regimen. Which of the following should adjustments be made to their therapy?
    a. No adjustments are necessary.
    b. Phenytoin dose should be decreased by 25 percent.
    c. Phenytoin dose should be increased by 25 percent.
    d. Felbamate dose should be increased by 15 percent
16. When considering the oxcarbazepine clearance rate in children, which of the following is most accurate?
   a. The clearance rate in children 2 to 4 years of age is less than that of adults by 40 percent.
   b. The clearance rate in children 4 to 12 years of age is less than that of adults by 80 percent.
   c. The clearance rate in children 4 to 12 years of age is higher than that of adults by 80 percent.
   d. The clearance rate in children 2 to 4 years of age is higher than that of adults by 40 percent.

17. Which of the following AEDs distributes into the kidneys and liver twice as much as in the tissues?
   a. Zonisamide
   b. Lamotrigine
   c. Levetiracetam
   d. Lamotrigine

18. Which of the following AEDs has the limiting side effects of aplastic anemia?
   a. Lamotrigine
   b. Topiramate
   c. Tiagabine
   d. Felbamate

19. Patients with a sulfonamide allergy should not be initiated on which AED?
   a. Gabapentin
   b. Zonisamide
   c. Levetiracetam
   d. Vigabatrin

20. The mechanism of which of the following AEDs irreversible inhibition of GABA transaminase?
   a. Tiagabine
   b. Lamotrigine
   c. Felbamate
   d. Vigabitrin

21. Is this program used to meet your mandatory C.E. requirements?
   a. yes  b. no

22. Type of pharmacist:  a. owner  b. manager  c. employee

23. Age group:   a. 21–30  b. 31–40  c. 41–50  d. 51–60  e. Over 60

24. Did this article achieve its stated objectives?  a. yes  b. no

25. How much of this program can you apply in practice?
   a. all  b. some  c. very little  d. none

How long did it take you to complete both the reading and the quiz? ______ minutes