Continuing Education

Epilepsy Treatment for Children and Adolescents

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Learning Objectives:

1. Define epilepsy and the different types of seizures.
2. Recognize risk of seizure recurrence after a withdrawal from medication.
3. Assess which medications are appropriate for the type of seizure.
4. Outline appropriate non-pharmacologic recommendations to a patient.
5. Potentially assist someone who is having a seizure, knowing what to do and not to do.

Introduction

Epilepsy is the third most common neurologic disorder after stroke and dementia, and it is a continuous battle that many people face in the U.S. today.[1] It is a disorder of the brain that is characterized by a predisposition of the cognitive, neurobiological, psychological, and social consequence to generate epileptic seizures. Epilepsy is classified as at least two unprovoked seizures that are separated by at least 24 hours.[2] Since there is no specific time frame beyond the 24 hours mentioned previously, clinical judgement is used to determine if the patient has epilepsy. Approximately 1% of the population has epilepsy, and 125,000 new cases are seen per year.[3] Around 30% of these cases include people under the age of 18 at the time they are diagnosed, and the other 70% of this population is diagnosed at an older age. Approximately 10% of the population will have at least one seizure in their lifetime. The likelihood of seizure recurrence within 2 years of the initial seizure is about 40% - 50% in untreated individuals.[4] The risk of a seizure is highest in newborns, young children, and patients older than 65 years of age. Central nervous system (CNS) disorders, such as trauma, meningitis, tumors, and exposure to toxins account for 30% of all seizures.[2] Seizures may also result from reversible causes including: infection/fever, alcohol withdrawal, metabolic disturbances, and concomitant medications.

Multiple factors contribute to seizure development including: excessive excitation, disordered inhibition of cortical neurons, and abnormal firing of those neurons. These factors can lead to a loss of normal conductance and inhibitory currents. Imbalances between the main neurotransmitters (glutamate, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, and acetylcholine) can contribute to seizure development as well. Glutamate is an excitatory neurotransmitter, while GABA is inhibitory. Excitation of these neurons can involve one hemisphere of the brain, which is referred to as focal seizures, or both hemispheres of the brain, which is classified as a generalized seizure.

Disruption of the normal stability of the neurons can trigger hyperexcitability and seizures. Medical conditions that can cause seizures include: cerebral palsy, head injury, mental retardation, neurodegenerative disorders (e.g. Alzheimer's disease), and stroke. Genetics can also impact seizures due to mutations or genetic predisposition in primary generalized epilepsy. There are also unknown causes, which are referred to as idiopathic etiology and cryptogenic etiology. Idiopathic is a term used when genetics is suspected. Cryptogenic is a term used when there is no obvious connection or if a focal onset seizure is the cause.

Focal seizures and generalized seizures are the two main classifications of seizures.[5] Focal seizures include simple partial (SP), complex partial (CP), and secondarily generalized seizure. Generalized seizures include generalized absence seizures, generalized tonic-clonic (GTC) seizures, myoclonic jerks, and atonic seizures. Table 1 describes each of these in detail. These seizures can define different types of syndromes as well, known as epilepsy syndromes.[2] Although there are many syndromes, there are five of particular interest: Juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, childhood absence epilepsy, reflex epilepsy, and temporal lobe epilepsy. Accurate diagnosis of syndromes can serve as a better guide for therapeutic recommendations. These syndromes are described in Table 2 below.

Table 1. Description of Seizure Types

Classification	Type of seizure	Description	Symptoms
Focal seizure	SP	• Seizures with NO loss of consciousness (LOC) • Auras serve as a warning sign • Asymmetric	• Motor symptoms (twitches) • Sensory/somatosensory (smelling things not present, hearing clicking/ringing, feeling of pins and needles, sensations with no obvious stimulus) • Autonomic - repetitive movements with no purpose (tapping, smacking, chewing, rapid blinking, or picking at objects) • Psychic symptoms (fear, anxiety, déjà vu)
	CP	• Alteration of consciousness that can progress to GTC and can be mistaken for psychotic episodes • Asymmetric	• Periods of memory loss • Aberrations of behavior • Motor symptoms • Sensory/somatosensory (smelling things not present, hearing clicking/ringing, feeling of pins and needles, sensations with no obvious stimulus) • Autonomic (tapping, smacking, chewing, rapid blinking, or picking at objects) • Psychic symptoms (fear, anxiety, déjà vu)
	Secondarily generalized	A partial seizure that becomes generalized	
Generalized seizure	Generalized absence	• LOC • Sudden onset usually interrupting ongoing activities	• Blank stare • Brief upward rotation of the eyes • LOC lasts for a several seconds • Mainly seen in children
	GTC	• LOC • Sudden sharp tonic contractions in the muscle followed by a period of rigid and clonic movements • Tonic and clonic seizures can occur separately	• Patient may cry or moan (Ictal cry) due to larynx and expiratory muscle contraction • Sphincter control is lost • May bite their tongue • Cyanosis may develop due to impaired respiration • After the seizure may: have altered consciousness, drowsiness, confusion (postictal period), and may frequently go into a deep sleep
	Myoclonic jerks	• LOC • Brief shock-like contraction of the muscles in the face, trunk, and extremities	• Contractions in one part of the body or the entire body • Isolated events or rapidly repetitive
	Atonic seizure	• LOC • Sudden loss of muscle tone that lasts 1-2 seconds	• Head drop • Dropping of a limb can occur • Slumping to the ground • Protective headwear may be needed for these patients in order to prevent trauma

SP-simple partial; CP-complex partial; LOC-loss of consciousness; GTC-generalized tonic-clonic

Table 2. Description of Epilepsy Syndromes

Type of syndrome	Seizure pattern	Comments
Juvenile myoclonic epilepsy (JME)	Myoclonic seizures that often precede GTC seizures and can usually happen upon awakening Absence seizures also common	Decreased sleep, fatigue, and alcohol can cause these seizures These account for 5% - 10% of all epilepsies High relapse rate
Lennox-Gastaut syndrome	Generalized seizures: myoclonic, atypical absence, tonic, and atonic/akinetic are most common An abnormal interictal EEG* with slow spike pattern	Cognitive dysfunction with mental retardation Over-sedation due to aggressive antiepileptic drugs (AEDs) may increase frequency Tolerance to benzodiazepines is common
Childhood absence epilepsy	Absence seizures usually in clusters of multiple seizures 40% is tonic-clonic Usual onset is age 4-8 years EEG shows classic 3-Hz spike-and-wave pattern	Good prognosis for remission Tonic-clonic seizures may persist Genetics plays a big role
Reflex epilepsy	Tonic-clonic seizures are the most common Photosensitivity is the typical inducer Reading can also induce partial seizures and may become generalized Underlying seizures may precipitate	Rare syndrome Precipitation of these seizures can occur from TV and video games
Temporal lobe epilepsy	Complex partial seizures with automatisms associated Auras are common with simple partial seizures About 50% of people move to secondary generalized seizures	Emotional stress can induce seizures Psychiatric disorders may be seen Surgical resection may be effective if patient identified as a good candidate

*EEG = electroencephalogram

Diagnosis

There are currently no laboratory tests for the diagnosis of epilepsy. However, laboratory tests are useful when treating a potentially contributing underlying condition (e.g. hypoglycemia, altered electrolyte, infections). Family members, school nurses, and teachers are an essential part in the diagnosis in children due to their witness of the seizure and their description of it. Recording the events of a seizure is extremely helpful when the onset, duration, characteristics, behavior, eye movement, and consciousness are documented and available. Other diagnostic methods include the use of computed tomography (CT), electroencephalogram (EEG), and magnetic resonance imaging (MRI). An MRI is useful for the diagnosis of a seizure, especially when imaging the temporal lobe, and it is preferred to a CT because it can locate brain lesions or anatomic defects. CT scans are typically not helpful, except

with the initial evaluation of the brain and when looking for tumors or bleeding. Approximately 50% of patients who have epilepsy will have an epileptiform EEG, which is reflective of a seizure. The EEG patterns consist of spikes, waves, and wave discharges either alone or accompanied by slow waves, occurring in bursts or single spikes that usually last a few seconds.[6] Therefore, an EEG is often useful for seizure identification.

Seizure Risk

Risk factors for seizure disorders include: hyperventilation, excessive sleep, deprivation of sleep, sensory stimuli, emotional stress, hormonal changes, perinatal injuries, and small gestational weight at birth.[2] Drugs can also produce a risk of seizure such as theophylline, alcohol, phenothiazines at high doses, antidepressants, and street drugs due to these medications lowering the seizure threshold. At this time, immunizations do not have a connection with seizures. There is also a seizure recurrence risk after withdrawing from AEDs. The risks of this occurring is more likely if the following are true:

- < 2 years seizure free before withdrawal
- Onset of seizures after age 12
- History of atypical febrile seizures, also known as a complex febrile seizure. These seizures differ from typical febrile seizure due to them lasting longer than 15 minutes.
- Family history
- Seizures not controlled until 2-6 years after diagnosis
- >30 seizures before control or >100 seizures total
- Focal seizures
- Absence seizure history
- Abnormal EEG throughout treatment
- Slowing on EEG before withdrawal
- Moderate to severe mental retardation
- Withdrawal of sodium valproate or phenytoin

General Approach to Treatment

The pharmacologic treatment of epilepsy is extremely individualized to a patient's seizure type or epileptic syndrome, their other medications and medical conditions, and their lifestyle.[7] The successful management of a patient's epilepsy depends on their understanding of their medical condition, education and adherence to medication(s), and collaborative practice between both practitioners and the patient themselves.

Therapy Initiation

Pharmacologic treatment is usually initiated after a patient experiences a second seizure, and a diagnosis of epilepsy is confirmed. While less common, patients may be started on AED therapy after the first unprovoked seizure if the patient has a neurological deficit, the EEG shows unequivocal epileptic activity, the patient considers the risk of having another seizure unacceptable, or brain imaging shows a structural abnormality. Initially, patients should be started on AED monotherapy with a preferred first line agent. Table 3 below lists appropriate and inappropriate AEDs that may be used for various seizure types or epileptic syndromes. If initial monotherapy treatment is unsuccessful, clinicians should try another monotherapy treatment option. If an AED failed due to an adverse drug event or continued seizures, a second line medication should be initiated and titrated to an appropriate or maximally tolerated dose, and the initial medication should be tapered off slowly. In the case that epilepsy is still not controlled, a second medication may be added to the first. If the second drug is not helpful, slowly withdraw one of the two medications prior to starting another option. The choice between which medication to withdraw is dependent upon relative efficacy, adverse drug reactions (ADR), and the how the patient tolerates the medications. If after a series of trials of combination regimens fail to control the patient's epilepsy the most effective previous regimen, whether it is monotherapy or combination therapy, should be used.

Table 3. AED Options by Seizure Type

Type	1st line AEDs	Adjunctive AEDs	Do not use (may worsen seizures)
Focal	Carbamazepine Lamotrigine [a] Levetiracetam Oxcarbazepine [a] Sodium Valproate [d]	Carbamazepine Clobazam Gabapentin [c] Lamotrigine Levetiracetam Oxcarbazepine Sodium Valproate Topiramate	
Generalized absence	Ethosuximide [a] Lamotrigine Sodium Valproate	Ethosuximide Lamotrigine Sodium Valproate	Carbamazepine Gabapentin Oxcarbazepine Vigabatrin(Sabril) Phenytoin Pregabalin (Lyrica) Tiagabine
GTC	Carbamazepine Lamotrigine Oxcarbazepine Sodium Valproate	Clobazam Lamotrigine Levetiracetam Sodium Valproate Topiramate	If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected: Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin (Lyrica) Tiagabine Vigabatrin (Sabril)
Myoclonic jerks	Levetiracetam Sodium Valproate Topiramate[a]	Levetiracetam Sodium Valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin (Lyrica) Tiagabine Vigabatrin (Sabril)
Atonic	Sodium Valproate	Lamotrigine	Carbamazepine Gabapentin Oxcarbazepine Pregabalin (Lyrica) Tiagabine Vigabatrin (Sabril)

[a] Not recommended in patients <2 years of age[8] [b] ER formulation not recommended in patients <10 years of age[8]
[c] Not recommended in patients <3 years of age[8]

Continuation of Pharmacologic Treatment

In order to enhance medication adherence, patients and caregivers should be educated about their conditions, medications, and their medication regimens should be as simplified as possible. While not a routine recommendation, blood levels may need to be drawn when adjusting a phenytoin dose, managing pharmacokinetic interactions, toxicity is suspected, non-adherence is a concern, or in particular clinical conditions such as status epilepticus or organ failure.

Therapy Withdrawal

There is a possibility that pharmacologic treatment for epilepsy may be withdrawn after an individual is seizure free for a period of two years. Patients, caregivers, and medical professionals should have a conversation at this time regarding the risks and benefits of discontinuing medication. AEDs should be withdrawn slowly (≥2 – 3 months), and one AED should be withdrawn at a time. While this discontinuation period is time consuming, it is important because it reduces the risk of seizure recurrence and harm.

Efficacy of Treatment in Clinical Trials

Many things must be taken into consideration when selecting an AED, including the type of seizure the patient is experiencing, the age of the patient, and what dosage forms can be taken. These considerations can lead to multiple choices that can be prescribed as initial medications. However, providers tend to prescribe newer medications before their safety and efficacy profiles have been established.[9] Newer drugs are

usually compared to placebo, and typically the FDA does not require it to be compared to older drugs that have been more frequently used. This lack of testing can lead to newer drugs being less efficacious and having a greater number of adverse reactions. An observational study done by *Bourgeois et al.*, has shown that first-generation AEDs (carbamazepine, ethosuximide, phenobarbital, phenytoin, or sodium valproate) and second-generation AEDs (carbamazepine extended release, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, sodium valproate extended release, or zonisamide) have similar therapeutic ranges and efficacy. First and second-generation drugs taken by patients had a similar 1-year retention rate of 26% (95% CI: 24%–28%) and 26% (95 % CI: 25%–28%), respectively. This study also showed that 26% (95% CI: 25%–28%) and 29% of patients (95% CI: 27%–31%), taking a first or second-generation AED respectively, had to restart therapy due to seizure recurrence after discontinuation of therapy. Another study, *Incecik et al*., showed that the recurrence rate of seizures within the first year was 23.7%, with the most pertinent risk factors being: etiology of epilepsy, mental retardation, febrile seizure, abnormal neuroimaging, abnormal first EEG, and total number of AEDs before remission.[10] Another pertinent factor with efficacy of treatment is through medication adherence which can be influenced by the ADRs associated with treatment.

Before an AED medication is chosen, the ADRs associated need to be assessed and taken into consideration so that each treatment can be individualized accordingly. Tailoring a patient's medication is vital to having effective therapy due to children with epilepsy being more prone to developmental delays, attention-deficit/hyperactivity disorder, conduct problems, autism/autism spectrum disorder, depression, anxiety, and headaches when compared to healthy children.[11] Somnolence and (nonspecific) behavioral problems are the most common ADRs, and these are more common in patients receiving polytherapy.[12] When prescribing, it is crucial to assess both the current problems and possible ADRs of the medication to properly treat the patient to produce the best possible outcomes.

Surgery and Non-Pharmacologic Options

One option for children with epilepsy, who continue to have seizures despite optimal medication is surgery.[13] While it may be considered an extreme measure, removing one part of the brain that is associated with seizure activity can solve this problem. A lobectomy is one type of surgery for children where a section of the brain that is producing the seizure is removed from the lobe. The most common lobectomy performed is a temporal lobectomy, and it has an 85% chance of improvement in seizure or stopping the seizures completely. Another option is multiple subpial transection surgery where cuts are made on the surface of the brain in specific parts that are causing the seizures. Corpus callosotomy is another surgery where the link between the two hemispheres of the brain is cut in order to prevent seizures from spreading. A hemispherectomy is another procedure where up to half of the entire brain is removed in order to help with the seizure. Lastly, laser interstitial thermal therapy may be an option.[14] It is a minimally invasive surgery for patients with drug-resistant epilepsy, and it uses heat to target and remove the region where the seizures originate.

If surgery is not an option or not something that is desired, vagal nerve stimulation (VNS) may be possible.[13] VNS is a newer treatment available that involves implanting a small device around the size of a silver dollar in the chest. The device is attached by small wires under the skin to the vagus nerve, which is a large nerve in the neck, and is programmed to emit pulses of electricity on a regular schedule to the nerve every few minutes. This helps to reduce the frequency or intensity of the seizure. Parents or the child can also trigger this to happen manually via a magnet that can be worn on the wrist or belt so that if an episode is about to happen they can wave the magnet over the device and trigger an electrical charge. Side effects may include hoarseness or discomfort as well as voice changes during an electrical discharge.

Another non-pharmacologic treatment option for children and adolescents with epilepsy refractory to AEDs is the ketogenic diet, which has been used to control seizures in epileptics for nearly 100 years.[7,15] While it is unknown exactly how the ketogenic diet reduces seizure occurrence, it is typically used as an adjunct to AED therapy and is characterized by ingesting a

high proportion of fats and low proportion of carbohydrates in a ratio of 4:1 or 3:1. When the body is depleted of carbohydrates the liver begins converting fat into fatty acids and ketone bodies which can be used as energy. Due to the lack of minerals and vitamins, individuals on this diet must take supplements to ensure proper nutrition.[16] In addition, some side effects of this diet include: constipation, lack of energy, and kidney stones. The ketogenic diet has shown at least a 50% reduction in the number of seizures in over half of children who adhere to this diet, with up to 10% - 15% of children becoming completely seizure-free. Overall, the diet seems to be well tolerated and efficacious in reducing seizure frequency, but should be carefully considered by patients prior to starting it due to the time and effort that this particular diet entails. While its efficacy in seizure reduction has been demonstrated, there are concerns regarding the long-term effects of this diet.[17] Due to these concerns, future research needs to be conducted in order to find other options in the treatment of epilepsy.

Future Research

Epilepsy is a heterogeneous disorder that has complex origins and to understand these gene–environment interactions, gene–gene interactions, and epigenetic mechanisms/DNA tags it need to be studied.[18,19] Understanding the gene-gene interactions is important because patients with epilepsy have family members with a higher risk of seizures than the general population. Epigenetic mechanisms is an area that concentrates on how different genes are expressed in the DNA and how these expressions can affect cells; thus causing a patient to be more likely to have epilepsy.[19] Other studies have suggested that epilepsy and comorbidities have a role to play, which suggests that specific forms of epilepsies will have certain comorbidities together.[18] Possible examples of these comorbidities are distinguishing the specific sleep disturbances and spectrum of cognitive and/or psychiatric problems in patients to better understand the uniqueness of their condition.

Epilepsy is currently being controlled in 50% - 60% of patients with either drugs or surgery, but curing epilepsy still remains a challenge. Some of the challenges that need to be overcome include: developing new therapeutics for refractory epilepsies, accurately localizing abnormal neural activity prior to seizures in patients with uncontrolled epilepsy, early identification of patients at risk for refractory epilepsy, and increasing the specificity of chemical and surgical treatments for epilepsy to maintain, enhance function, and minimize/eliminate side effects. New technology is being developed to further specify and to “pin point” the problem. For example, microelectrode arrays, which record individual action potentials from a hundred or more neurons simultaneously, have greater sensitivity and spatial resolution than EEGs. Another technology being developed is a method using EEGs in order to detect seizures before they occur and to prevent them before they become harmful without the patient knowing. Lastly, the future of implantable devices, nanotechnology, delivery of stem cells, and molecular therapies depends on accessing the brain safely with tissue compatible sensors and also bridging biology with science technology.

If it is not possible to find a cure in the future then preventing, modifying, or stopping the disease progression may be possible.[20] Gene-gene expression (family links), gene-environment expression (response to AEDs), and epigenetic mechanisms (gene expression) are promising for the future of patients with epilepsy and continue to be an area of interest. Currently, the best plan of action is to properly diagnose the specific type of seizure and comorbidities, then tailor the medication regimen to give the patient the best quality of life.

Role of Pharmacists

Pharmacists play an essential role in the treatment of epilepsy. As healthcare professionals, pharmacists are not there just to fill medications for patients who present to the pharmacy with prescriptions, but we are also there to evaluate and counsel them on their therapy.[21] Evaluating a medication and noticing its use and other indications allows for us to counsel the patient properly. Counseling should include information about adherence, avoidance of triggers (e.g. too much/little sleep, stress, alcohol, and photosensory stimulation), goals of therapy, self-management, side effects of the medication(s), and even food and water intake with their medications. If monitoring is required for the patient instructions on frequency of monitoring, steps of monitoring, and the goals are

things to provide to the patient. Pharmacists also have a major role in detecting drug interactions as well as understanding the pharmacokinetic properties of the drugs. If adherence is a problem for a patient, a pharmacist can evaluate the situation and see if money, pill burden, or a side effect may be the problem with adherence. Whether it's finding coupons/incentives/patient assistance programs to help with cost, interacting with the insurance company, switching to an extended formulation, or talking to the doctor in order to switch the medication altogether, a huge impact can be made in order to increase adherence. These are all areas where a pharmacist can intervene and make changes in order to improve patient outcomes.

Another role pharmacists may have is helping a patient that is having an active seizure. Some typical things to do when someone is having a seizure and things NOT to do are included in Table 4 below.[23]

Table 4. Active Seizure Recommendations

What you should do	When to call 911	What NOT to do
1. Help the person to the floor 2. Gently turn the person onto one side in order to help them breathe 3. Remove anything hard or sharp from the area to prevent injury 4. Place something soft and flat under their head 5. Remove eyeglasses 6. Loosen anything around their neck that may make it difficult to breathe 7. Time the seizure	• The person has never had a seizure before • The person is having difficulty breathing or waking after the seizure • The seizure lasts more than 5 minutes • The person has another seizure closely after the first one • The person is injured during the seizure • The seizure happens while in water • The person has a health condition (ex. diabetes, heart disease, pregnancy)	• Do **not** hold the person down or try to restrain his or her movements • Do **not** put anything in their mouth • Do **not** try to give CPR • Do **not** offer water or food until they are fully alert

Conclusion

Epilepsy is an ongoing problem in the U.S. today and as pharmacists, we are in a unique position to help these patients. Because the majority of patients are diagnosed with epilepsy during childhood, it is vital that pharmacists and caregivers are aware of the signs and symptoms in order to optimize patient outcomes through diagnosis and medication management. Multiple therapy options are available for children and adolescents in order to control their seizures. There are also non-pharmacologic options currently available to treat those patients that need adjunctive therapy. Future research may provide further insight into epilepsy management and increase the quality of life for these children and adolescents with this condition.

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