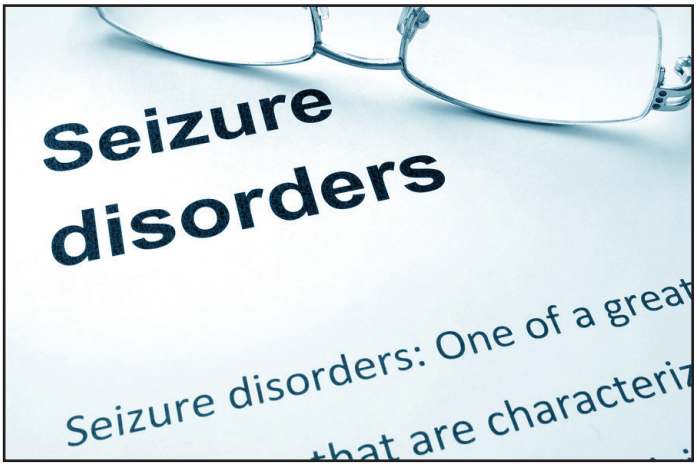
PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

"Seizure Disorders"

January 2017



This is the beginning of CE PRN's 39th year. WOW! Thanks for your continued participation.

The primary goal of seizure disorder treatment is to achieve a seizure-free patient. We update this topic often because it's so important. This lesson provides 1.25 (0.125 CEUs) contact hours of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 0798-000-18-228-H01-P for pharmacists & 0798-000-18-228-H01-T for technicians.**

Participants completing this lesson by December 31, 2019 may receive full credit. Release date for this lesson is January 1, 2017.

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 participants will be able to:

Pharmacists:

1. Describe the epidemiology of seizure disorders.
2. List the types of seizures.
3. Discuss the goals associated with treating seizure disorders.
4. List factors that affect the selection of anticonvulsants.
5. Define the mechanism of action of the various anticonvulsants.
6. Evaluate ketogenic treatment of seizure disorders.

Technicians:

1. List the types of seizures.
2. List factors that affect the selection of anticonvulsants.
3. Evaluate ketogenic treatment of seizure disorders.

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INTRODUCTION

Seizure disorders are a chronic group of neurological diseases characterized by episodes of abnormal, unorganized, electrical activity that takes place in the cortical gray matter of the brain and temporarily disrupt and interfere with normal charges in the brain. Such unprovoked and unpredictable disruption in the electrical brain activity may lead to transient attacks of unusual sensation, confusion, lack of awareness of surroundings, unconsciousness and physical convulsions. The terms epilepsy and seizure are often used interchangeably as there is no difference between the two. However, convulsions, confusion and lack of awareness of surroundings as a result of health problems such as fever, head trauma, and brain cancer are not considered epilepsy. Symptoms of seizures vary from one patient to another, but for the most part depend on the source of the abnormal condition(s).

EPIDEMIOLOGY

Seizure disorders affect approximately 1% of the population and each year they account for over $10 billion in health care costs. They are the fourth most common disorder after migraine headache, stroke, and Alzheimer's disease. The occurrence is higher among young children and older adults. It is estimated that an initial seizure occurs in over 300,000 persons annually. About 120,000 of these are less than 18 years of age, and 75,000 to 100,000 are children less than 5 years old. The annual number of new cases is about 200,000, 45,000 of which are children younger than 15 years of age. The peak incidence occurs among babies younger than 2, and the elderly over 65 years old. Incidence among males is slightly more than females. About 70% of patients may become seizure free for 5 years with medications and 75% of these who are taking medications for 2-5 years can discontinue taking medications. The incidence

increases with advancing age. About 300,000 patients over 65 years of age exhibit seizure disorders. A study conducted in 17 states between 2003 and 2011 indicated that the annual mortality rate of patients with seizure disorders was 16,891 per 100,000 persons, and this is 22% higher than in the general population without seizure disorders. Mortality rate among patients has been estimated to be 1.6 to 9.3 higher than in the general population. The direct cause of death is due to underlying neurologic disorders as well as sudden unexpected death due to status epilepticus seizure, accidental death during the course of the attack such as trauma, drowning, choking, suicide or mistreatment. Sudden unexpected death accounts for 8-17% of deaths among patients with disorders. About 1 out of 1000 patients die from sudden unexpected disease related situations. However, if treatment is delayed or the attack becomes uncontrollable, the mortality rate increases to 1 out of 150. In 2003 sudden unexpected deaths occurred in 116,000 patients. Approximately 5-10% of people experience a seizure without a cause by the age of 80 and the risk of developing a second attack is between 40% - 50%. In spite of the fact that patients respond well to drugs, especially the newer ones, approximately 30% to 40% of patients experience seizures.

TYPES OF SEIZURE DISORDERS

All states, as well as the District of Columbia and Puerto Rico, permit pharmacists to administer Seizures can be categorized into two major types: **focal and generalized**. These types differ mainly in how and where in the brain the distributed discharges begin. They can be short in duration, and difficult to notice or long attacks of strenuous trembling, falls and loss of consciousness.

FOCAL SEIZURES

These are also called **local** or **partial**. They occur in one of the four areas of the brain.

Focal seizures can be subdivided into two subtypes: **simple** and **complex**.

SIMPLE FOCAL SEIZURES

Simple focal seizures can be further classified into three groups: **simple motor, simple sensory and simple psychological**. The common denominator of these three subgroups during a seizure is that the patient is aware of his/her surroundings. They are very short in duration.

Simple Motor Focal Seizures affect the muscles and are exhibited by jerking, muscular rigidity and spasms in part of the body. It also may affect speech or automatic hand movement. Such abnormalities may remain on one side of the body or spread to the entire body.

Simple Sensory Focal Seizures involve any changes in the senses such as vision, hearing, smell, taste or touch. An aura, which is manifested by the perception of an unusual light, an unpleasant smell or confusion, may occur before the actual seizure begins.

Simple Psychological Focal Seizures involve emotion such as fear, anger, elation and anxiety.

COMPLEX FOCAL SEIZURES

During a complex focal seizure, the patient loses awareness of the surroundings or consciousness. Symptoms such as lip smacking, picking at clothes, making small movements, especially of the hands and feet due to nervousness, impatience and restlessness may occur. The seizure usually lasts from several seconds up to two minutes. The patient is unresponsive and cannot recall the event.

GENERALIZED SEIZURES

Unlike focal seizures, and as the name indicates, generalized seizures involve all parts of the brain and the electrical discharges can begin from anywhere in the brain.

There are seven common types of generalized seizures:

1. Absence, formerly known as petit mal
2. Tonic-clonic or convulsive, formerly known as grand mal
3. Atonic, also known as drop attacks
4. Clonic
5. Tonic
6. Myoclonic
7. Status epilepticus

1. **Absence seizures** cause a brief loss of consciousness that may last for a few seconds and are usually accompanied with a few or no symptoms. They are most common among children. Following the onset of the attack the patient stops the ongoing activity and stares blankly with rapid blinking. The episode may start and end abruptly without realization of what has happened. During the attack the patient may stop talking, walking, reading, but resume the activity a few seconds later. The patient does not fall, and when the attack expires the patient is awake and thinks normally, but is not aware of the seizure.

2. **Tonic-clonic seizures** are characterized by unconsciousness, convulsions and muscular rigidity. The patient may fall to the ground and experience muscular jerks or spasms. The attacks occur in two phases: the **tonic phase** and the **clonic phase**. The **tonic phase** is characterized by a quick loss of consciousness and is followed by a sequence of muscular contractions and relaxation, especially the limbs, which appear as jerking movements that cannot be restrained. In the **clonic phase** the patient becomes unconscious and may fall. This is followed by convulsions ranging from twitching of the hands and legs, to strong shaking. The eyes may roll back and the jaw stiffens. This activity may last from one to two minutes after which the patient falls asleep due to exhaustion. During the attack, injuries, such as trauma to the head or tongue may occur, along with involuntary urination.

3. **Atonic seizures** are characterized by a brief drop in muscular tone resulting in weakness in various muscles. The eyelids may droop, neck muscles may fail to support the head, and, if standing, the legs may temporarily buckle. Duration of attack is around 30 seconds.

4. **Clonic seizures** consist of a rapid repeated jerking of muscles as a result of an alternating contraction and relaxation process. This movement lasts from a few seconds to a minute.

5. **Tonic seizures** occur when the normal tone of the muscles causes stiffness of the body, arms and legs. The patient remains conscious, but the seizure usually occurs during sleep. Duration of a tonic seizure is about 20 seconds.

6. **Myoclonic seizures** may be experienced by patients with seizure disorders or by undiagnosed individuals. These are characterized by a brief twitching of a muscle and lasts 1 to 2 seconds. They may occur in normal patients who are about to fall asleep.

7. **Status Epilepticus** is a serious, prolonged convulsive attack that can be life-threatening unless treated promptly. It involves a number of seizures that follow one another within a period of about 5 minutes without recovery of consciousness. In the past, for the attack to be considered as status epilepticus, it had to last for 20 minutes or more. Currently the criteria have changed slightly, and it must last for five minutes or more. Status epilepticus can be **convulsive** or **nonconvulsive**. A convulsive attack is considered an emergency medical problem if it is an extended attack or repeated tonic-clonic seizures without regaining consciousness from the initial attack. The patient may have after-effects. In non-convulsive status epilepticus, the patient experiences a long or repeated absence of seizures or complex focal seizures without loss of consciousness. The patient appears restless, unable to think clearly and unaware of the surroundings. Length of nonconvulsive status epilepticus seizures is inconsistent.

TREATMENT GOALS

There is no cure for a convulsion disorder, but there are medications that are capable of reducing the intensity and frequency of attacks, thereby keeping symptoms under control.

The primary goal of treatment is to achieve a seizure-free patient. The following factors need to be considered:

1. Selection of the proper medication. Choice of the appropriate drug may successfully assist in reduction or complete control of symptoms.

2. Choosing drug and the dose is essential. A rational approach is starting with a single drug at a low dose which could be gradually increased until the seizures are under control. Many medications possess side effects, and some are intolerable. It has been estimated that 60% of patients can become seizure free by using drugs with tolerable side effects.

3. Monotherapy is preferred over polytherapy due to the risk of drug interactions. Adverse effects along with the pharmacokinetics of the drug must be taken into consideration.

4. Age of patients as well as medical conditions are factors to be considered in the drug therapy.

5. Patients, physician and pharmacists must be aware that seizures may occur due to resistance to treatment.

6. Dealing with the psychological problems that patients face is essential. Following diagnosis, most patients live in fear of seizures. Many patients should participate in psychological counseling conducted by a neurologist, psychiatrist or psychologist.

EXPLANATION OF FACTORS FOR SELECTION OF ANTI-CONVULSION MEDICATIONS

1. Type of seizure: As indicated earlier, there are a number of seizure types that affect patients, each with a different etiology, set of characteristics and adverse effects.

2. Adverse effects of the selected drug should be minimal at an effective dosage and should be tolerated by the patient.

3. Selected drug should have no or minimum risk of causing any interaction with other drugs that may be used for treating comorbidity.

4. Some anticonvulsant drugs act centrally, and there is risk that behavior changes may occur. Educating the patient and members of the family about such risks is essential in improving the quality of the patient's life.

5. Cognitive effects: Cognition relates to the process of intellectual and conscious mental activity such as understanding, thinking, reasoning, remembering and learning. Cognition may detrimentally be affected by anticonvulsants resulting in disruption of the well-being of the patient and failure of therapy.

6. Patient's age can potentially affect the ability of a drug to provide optimal activity. Differences in the pharmacokinetic parameters (including absorption, metabolism and elimination) may affect the magnitude of seizure control.

7. Childbearing potential: This is an important fact. Use of anticonvulsants is risky as they may impact upon the fetus.

8. Comorbidity: The coexistence of seizures with other disorders such as brain tumor, cardiovascular conditions, previous seizures, liver disease, head trauma, history of traumatic epilepsy, and metabolic disorders can complicate the selection of the appropriate drug.

MECHANISM OF ACTION OF ANTI-SEIZURE MEDICATIONS

The use of anticonvulsants is typically intended for long-term therapy. Initial dosing usually starts with one drug, and then changing dosage as needed. Failure of one-drug therapy (monotherapy) may require replacement by another drug. When doing so, care must be exercised. The use of the first drug and the selected new drug should overlap for a few days. Another option is to add another drug (or drugs) (polytherapy). Such therapy may become permanent. Polytherapy has been shown to increase effectiveness of treatment and reduce adverse effects as the dose of each drug is often reduced. Abrupt discontinuation of anticonvulsants may trigger resumption of seizures that may be stronger than the original ones.

Anticonvulsant mechanisms of action may include:

1. Sodium channel blockade
2. GABA – receptors activation (agonists)
3. GABA reuptake inhibition
4. GABA transaminase inhibition
5. Anticonvulsants that have potential of acting like GABA
6. Glutamate blockade
7. Neuronal potassium channel openers

Sodium Channel Blockade

Voltage-gated ion channels are transmembrane protein channels that are passages specific for ions such as sodium, potassium and calcium and are sensitive to voltage or electrical charges in the cell membrane potential. The protein channels can open and close in response to changes in the electrical potential across a membrane. Sodium and potassium-gated channels are slightly permeable to these ions, but are variably permeable to calcium ion. Sodium channels are the main cause of depolarization and repolarization of nerve membranes during action potential. During an action potential, the channels become active and allow

entry of ions. Once activation ceases, a good portion of these channels are inactivated for a refractory period, and as such exist in the inactive form resulting in prevention of propagating action potential. Sodium channel blocker anticonvulsants are capable of preventing these channels from becoming active. As a result, they prevent high-frequency firing of the axons.

Examples of Sodium Channel Blockers

As a sodium-channel blocker, **phenytoin** is capable of suppressing the tonic phase but not the clonic phase. GI absorption varies from one individual to another but usually it is moderately fast. Its protein binding rate is about 90% and metabolism is hepatic in nature. It tends to increase the blood concentration of the following drugs when given in combination with: NSAIDs, cimetidine, miconazole and isoniazid. Phenytoin acts as an enzyme inducer and as such it increases the breakdown of vitamin D, folic acid, cortisol, vitamin K and oral contraceptives. Except for absence and myoclonic seizures, phenytoin is used for all other types of seizures. Adverse effects include ataxia, dizziness, diplopia, nausea, gingivitis, increased risk of birth defects and anemia.

Carbamazepine is chemically related to tricyclic antidepressants, but pharmacologically has action similar to phenytoin. It is indicated for focal seizures, especially temporal or psychomotor ones, as well as generalized seizures. It is used in facial neuralgia therapy. Adverse effects include blurred vision, drowsiness, ataxia, dizziness, hepatitis, leukopenia and thrombocytopenia, which requires monitoring of blood count.

Oxcarbazepine is related to carbamazepine and has the same therapeutic activities and adverse effects.

Lamotrigine has a triazine structure and due to its sodium channel blockade activity, it lowers aspartate and glutamate presynaptic release. Lamotrigine is used in treating focal as well as tonic-clonic seizures that do not respond to usual therapy. It may be used alone or in combination with other medications. Side effects include diplopia, dizziness, and neurosensory symptoms.

Valproic Acid and Valproate: Due to its inhibition of sodium channels, it causes polarization of the axons and lowering excitability. It also increases level of GABA. It is used in many types of seizures, including absence, focal and generalized. Side effects include nausea, dizziness, hair loss, blurred and double vision, tinnitus, and changes in menstrual cycle. It is one of the most common anticonvulsants.

Primidone has similar indications as phenobarbital. After absorption, primidone is metabolized to phenobarbital. It is not the anticonvulsant of first choice due to its potent sedative affect that is similar to phenobarbital. It may be used in control of partial or secondary generalized seizures.

Ethosuximide reduces excitability of neurons probably by blocking ion channels especially the calcium channels. It is the anticonvulsant of choice in the treatment of childhood and juvenile absence seizures. Side effects include nausea, vomiting, GI disturbance, appetite loss, weight loss, dizziness and drowsiness.

Examples of GABA-Receptor Agonists (Enhancers)

A seizure is usually triggered when the excitatory activity within the brain exceeds inhibition. The neurotransmitter in the brain responsible for inhibiting activity is GABA, whose receptors have different binding sites for benzodiazepines and barbiturates. After binding to the receptor sites,

GABA receptor agonists exert their action. The most widely used benzodiazepines for seizure disorders are lorazepam, diazepam, clonazepam, and clobazam. Lorazepam and diazepam have rapid and strong anticonvulsant activity. They are normally used for emergencies but not for long-term therapy due to the development to tolerance.

Clobazam is approved as an add-on drug in treating seizures. It acts as a GABA receptor agonist and may block sodium channels. It is effective in suppressing complex partial seizures. A drawback of clobazam is the development of tolerance. Side effects include sedation, dizziness, ataxia, blurred vision, irritability, depression and muscular weakness.

Clonazepam is utilized in the treatment of all types of focal seizures. It is not recommended for use as an add-on drug for treating refractory epilepsy due to its sedative action and development of tolerance. It binds to GABA receptors.

Phenobarbital is an effective anticonvulsant and was used as such decades ago. However, it fell out of favor due to adverse effects such as sedation and potent hepatic microsomal enzyme induction. Additionally, there are new generations of more effective and safer anticonvulsants that are currently available. Other adverse effects include cognitive and behavioral changes, depression and ataxia. This drug acts by increasing the flux of the chloride ion in the neuron thereby reducing excitation, and also by enhancing GABA's.

Example of GABA Reuptake Inhibition

Tiagabine is used as an add-on drug for control of partial seizures and anxiety disorders in teenagers and older patients. Its mechanism of action is not clear but it is **related to nipecotic acid which is a GABA reuptake inhibitor. It also tends to inhibit** GABA transporter-1 (GAT-1). Adverse effects include dizziness, nervousness and memory impairment.

Example of GABA-transaminase Inhibitors

Vigabatrin: The enzyme GABA-transaminase tends to metabolize GABA found in the extracellular compartment. Increased level of GABA occurs when GABA-transaminase is inhibited. The increase in the level of the inhibitory neurotransmitter GABA in the neurons of cortex causes reduction of neuronal excitability. Vigabatrin assists in increasing the level of GABA by inhibiting the enzyme GABA-transaminase. Vigabatrin is used in patients 10 years of age and older as add-on drug in patients with refractory (resistant) complex partial seizures that fail to respond to therapy and for whom the potential benefit outweighs the risk of vision loss. It is not effective against generalized tonic-clonic and absence seizures. The drug may worsen myoclonic seizures.

Anticonvulsants that have Potential of Acting Like GABA

These are anticonvulsants that have the potential of acting like GABA. Glutamic acid is an amino acid needed in the biosynthesis of protein. An enzyme known as glutamic acid decarboxylase (GAD) acts to catalyze the conversion of glutamate to GABA. Certain anticonvulsants have an effect on GAD and as a result increase GABA levels.

Gabapentin: In spite of the fact that gabapentin has a structure similar to that of GABA, it does very little to stimulate GABA receptors. However, it increases the intracellular level of GABA via a mechanism that is not understood. Gabapentin does not bind to plasma protein and does not stimulate hepatic enzymes. Therefore, it is eliminated from the body unchanged. The drug is used in higher doses for control of partial and secondarily generalized tonic-clonic seizures. It is ineffective in myoclonic attacks as well as in most generalized seizures. Adverse

effects include skin rash, dizziness, ataxia, nystagmus, headache, and fatigue. Tremors have occurred in high doses.

Pregabalin is used as an add-on drug in the control of epilepsy caused by partial seizures with or without secondary generalized seizures in patients 18 years of age and older. It is also used for neuropathy from fibromyalgia, shingles or diabetes. Side effects include blurred vision, dizziness, constipation, drowsiness, dry mouth, headache, fatigue, numbness, tingling and confusion.

Examples of Glutamate Blockade Drugs

Felbamate is a meprobamate-like drug that has a potent anticonvulsant activity and is effective for various types of seizures, especially refractory, partial seizures. While its mechanism of action is not completely understood, it is believed to block voltage-gated calcium and sodium channels, NMDA (N-methyl-D-aspartate) receptors, which are glutamate receptors, and ion channel protein found in nerve cells. In spite of its effectiveness, its approval for general use was withdrawn due to occurrence of aplastic anemia and liver failure. Its prescribing is limited to neurologists for patients where potential benefit outweighs the risk.

Topiramine is a potent anticonvulsant whose structure is derived from D-fructose. It has multiple mechanisms of action. In addition to being a sodium channel blocker it acts as a non-NMDA glutamate receptor inhibitor as well as a GABA enhancer. It is used as an add-on drug in drug-resistant generalized convulsion disorders including juvenile myoclonic, absence and generalized tonic-clonic seizures. Side effects include ataxia, lack of concentration, dizziness and confusion. It may cause weight loss.

Example of Neuronal Potassium Channel Opener

Ezogabine is a potassium channel opener with action different from other anticonvulsants. It was approved by the FDA in 2011 as an add-on drug for partial seizures which do not respond to other anticonvulsants. Side effects include dizziness, tinnitus, vertigo, confusion and slurred speech.

KETOGENIC DIET—DIETARY TREATMENT OF EPILEPSY

Ketosis is a nutritional metabolic process that occurs as a result of fasting or consumption of food very low in carbohydrates and very high in fat. When fat is used as the main source of caloric intake, ketone bodies are formed in the blood plasma. Ketone bodies are water soluble chemicals (acetoacetate, beta-hydroxybutyrate, and acetone) that are generated by the liver as a result of breakdown of fat that is used for energy.

Dietary treatment of epilepsy is a century old concept that lost its application due to its ineffectiveness and the discovery of anticonvulsants that are capable of controlling seizures. However, utilization of diet for treating epilepsy, especially in children, has recently been revived through the use of a ketogenic diet. Ketogenic diet refers to a high percentage of fat and very low percentage of carbohydrates. The diet may provide 3-4 grams of fat for every 1 gram of carbohydrate. Also, it provides 75-100 calories for every kg of body weight and 1-2 grams of protein per kg of body weight. Ketogenic diet is aimed at children whose generalized seizures fail to respond to anticonvulsants. Dietary modification begins after a period of fasting that results in production of ketones. This period requires a stay in the hospital to monitor the risk of occurrence of adverse reactions, some of which could be serious. At the end of the first two months, the diet is officially evaluated. If there is improvement, in seizure

occurrence (reduction), the diet is continued for a limited time period. Sources of fat include butter, fat-rich whipping cream, mayonnaise and vegetable oils. No carbohydrate should be consumed. Adverse effects of ketogenic diet include acidosis, hyperlipidemia, kidney stones, heart burn, and growth suppression in children. The efficacy of ketogenic diet for treating convulsive disorders lacks control studies and most of the results are based on case reports. Extreme care must be taken when this treatment option is used. It is risky.

SUMMARY & CONCLUSION

Seizures are a common chronic neurological disorder that affect over 1% of the population. There is no cure, but there are medications that are capable of controlling the severity and frequency of the seizures. Occasionally, patients become seizure-free for extended periods. Several convulsion disorders exist that can be treated with various anticonvulsants.

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SC 29579

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Contributing Faculty/Authors

Farid Sadik, PhD
Dean Emeritus University of South Carolina
College of Pharmacy
Columbia, SC
Adjunct Professor
Presbyterian College
School of Pharmacy

Executive Editor
William J. Feinberg, RPh, MBA

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1. Does the program meet the learning objectives?
   - Describe the epidemiology of seizure disorders — YES NO
   - List the types of seizures — YES NO
   - Discuss the goals associated with treating seizure disorders — YES NO
   - List factors that affect the selection of anticonvulsants — YES NO
   - Define the MOAs of the anticonvulsants — YES NO
   - Evaluate ketogenic treatment of seizures — YES NO

2. Was the program independent & non-commercial? YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

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QUESTIONS

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1. **Which of the following is true?**
   A. Seizures are more common in females
   B. There are approximately 3 million patients in the U.S. with seizure disorders
   C. About 25% of seizure patients become seizure – free for 5 years with medications
   D. As patients become older, risk of developing seizure disorders becomes less

2. **Grand mal seizure disorder is now known as:**
   A. Status epilepticus
   B. Myoclonic
   C. Atonic
   D. Tonic – clonic

3. **Which type of seizure disorder causes a brief loss of consciousness that may last for a few seconds with no symptoms?**
   A. Atonic
   B. Tonic
   C. Clonic
   D. Absence seizure

4. **Which of the following is NOT a factor in selecting an anticonvulsant?**
   A. Mode of administration
   B. Cognitive effects
   C. Age
   D. Type of seizure

5. **Phenytoin acts by which of the following mechanisms?**
   A. GBA receptor agonist
   B. Glutamate blocker
   C. Sodium channel inhibitor
   D. GABA transaminase inhibitor

6. **In addition to being an anticonvulsant drug, carbamazepine is used in treating:**
   A. Facial neuralgia
   B. Pain associated with shingles
   C. Drug withdrawal therapy
   D. Alzheimer's disease

7. **Which of the following anticonvulsant drugs has a structure similar to D-fructose?**
   A. Ezogabine
   B. Felbamate
   C. Topiramine
   D. Valproate

8. **The potential adverse effect of a ketogenic diet is:**
   A. Dizziness.
   B. Acidosis
   C. Tinnitus
   D. Constipation

9. **Which of the following statements is TRUE about status epilepticus?**
   A. It is characterized by a brief twitching of a muscle
   B. It is always accompanied by convulsions
   C. The attack consists of a number of seizures that follow one another
   D. The seizure lasts for hours or days

10. **What is the treatment of choice for absence seizures?**
    A. Phenobarbital
    B. Ethosuximide
    C. Egogabin
    D. Phenytoin