Seizures and Epilepsy Syndromes

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Kelley M. Anderson, PhD, RN, FNP, received her undergraduate education at the University of Virginia. She completed her master's degree at the University of Texas, Austin, her post-master's family nurse practitioner education at the University of Florida, and her doctorial degree from the Catholic University of America in Washington, DC. While at the University of Florida, she worked with epileptic patients in the outpatient and acute care settings. She provided care with conventional modalities and assisted in the management of patients under investigative research medications and protocols.

Faculty Disclosure

Contributing faculty, Kelley M. Anderson, PhD, RN, FNP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all physicians, nurses, and other healthcare professionals who have contact with patients with seizure disorders.

Accreditations & Approvals

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A complete Works Cited list begins on page 64.

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Course Objective

The purpose of this course is to expand the understanding of seizure disorders for physicians, nurses, and other healthcare professionals in order to facilitate earlier diagnoses and more effective treatment.

Learning Objectives

Upon completion of this course, you should be able to:

1. Differentiate between a seizure and epilepsy.
2. Recall the incidence of epilepsy.
3. Identify the major etiologies of epilepsy.
4. Describe the phases of a seizure and exacerbating factors.
5. Define the major seizure classifications and seizure types.
6. Discuss the significance of history taking and differential diagnosis in identifying epilepsy.
7. Identify diagnostic studies useful in the care of patients with epilepsy.
8. Detail the management of epilepsy in specific populations.
9. Discuss advantages and disadvantages for the most commonly prescribed pharmacologic agents.
10. Describe nonpharmacologic treatments for epilepsy.
11. Identify the most common complications occurring during or after a seizure.
12. Explain the emergent treatments for status epilepticus.
13. Discuss the prevention of epilepsy and epilepsy-related injury, including specific patient education needs for non-English-proficient patients.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

It is common in many medical settings to encounter individuals with epilepsy or to be in contact with their families. The purpose of this course is to expand the understanding of seizure disorders for physicians, nurses, and other healthcare professionals in order to facilitate earlier diagnoses and more effective treatment. This course will provide basic information about epilepsy and its management and note additional education resources for patients with seizure disorders. Important features of the care of the patient with epilepsy will be presented. This will include an overview of the incidence and etiology of epilepsy, treatment modalities, prevention, and self-care management. The impact of epilepsy on the individual, family, and community will also be discussed. Finally, special epilepsy concerns, including psychosocial issues, will be reviewed.

OVERVIEW OF SEIZURES AND SEIZURE DISORDERS

Seizures are common neurologic disorders that occur across the entire spectrum of age, gender, race, and socioeconomic background. As a result, professionals in most healthcare professions will have contact with or care for individuals who experience seizure events. Understanding seizure treatment and management will assist all healthcare professionals to provide the most appropriate care for this patient population.

DEFINITIONS

In the mid-1800s, a seizure was described as an abnormal electrical discharge of the brain [1]. This description continues to typify our conceptualization of the definition of seizures. A seizure is a finite event of altered cerebral function because of excessive and abnormal electrical discharges of the brain cells [2]. This activity can interrupt the ongoing mental and behavioral activities of the individual. In general, a seizure is characterized by a transient alteration in cognizance and/or control over physical processes [2]. The alterations in brain activity occur suddenly. These disturbances may cause changes in awareness, bodily movements, sensations, and/or emotions [3].

A seizure may be a symptom of central nervous system (CNS) irritability due to a non-neurologic disorder or medical illness. There are many examples of these extra-cranial disorders, including: metabolic disturbances or disorders (e.g., diabetes); substance abuse; dehydration and water intoxication; liver, kidney, cardiac, or pulmonary disease; hypertension; septicemia; fever; and trauma [4]. If a seizure ceases when the systemic or metabolic condition is corrected, it may be considered a symptom of the underlying disorder. In these cases, the patient is not considered to have epilepsy.

The word epilepsy is derived from the Greek word *epilambanein*, meaning to attack or seize [3]. Conceptually, epilepsy is defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition" [5]. An isolated seizure does not indicate epilepsy. Approximately 7% to 8% of American adults will experience a seizure in their lifetime [2]. The majority of these seizures, however, are attributable to a specific cause, such as those mentioned above. Epilepsy, in contrast, is a recurrent illness [3]. It is a paroxysmal neurologic disorder consisting of recurrent episodes of alterations in level of consciousness, convulsive movements or other motor activity, sensory phenomena, behavioral abnormalities, and mental impairment. In clinical practice, epilepsy is considered to be present if any of the following conditions are present [6]:

- At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years [6].

Unfortunately, the word "epilepsy" is often inappropriately used as a generic term to describe disorders in which patients experience seizures. Compared to the 7% to 8% of Americans who will experience a seizure event in their lifetime, less than 2% of the adult population will be diagnosed with epilepsy [2; 7].

Seizures Classification and Terminology

In the last several decades, there have been significant changes made to the classification/terminology of seizures and epilepsies. The International League Against Epilepsy (ILAE) updated the original 1960 classification of seizures and epilepsies in 1981 and 1989, but the information contained in those updates had not been subsequently reviewed until 2005–2009 [8]. The 2010 report by the ILAE commission on classification and terminology reflected new understandings and investigative techniques (e.g., modern neuroimaging, genomic technologies, and concepts in molecular biology) that emerged since the 1980s updates.

In 2015, the ILAE established a Seizure Type Classification Task Force to prepare recommendations for a revised classification of seizure types. Revision of the 2010 classification scheme was motivated by several factors, including [9]:

- Some seizure types (e.g., tonic) can have either a focal or generalized onset.
- Lack of knowledge about the onset makes a seizure unclassifiable and difficult to discuss with the 1981 system.
- Retrospective seizure descriptions often do not specify a level of consciousness, and altered consciousness, though central to many seizures, is a complicated concept.
- Some terms in current use do not have high levels of community acceptance or public understanding (e.g., psychic, partial, simple partial).
- Some important seizure types are not included.

In 2017, the ILAE released an updated version of seizure-type classification (***Table 1***) [9; 10]. The updated ILAE classification scheme includes a "basic" and an "expanded" version of seizure types [10]. Use of one versus the other depends on the desired degree of detail. Seizure types are divided broadly into three groups: focal seizures, generalized seizures, and unknown [8]. Seizures not categorized as focal or generalized are categorized as onset unknown. The revised classification scheme is intended for practical clinical use among clinicians caring for people with epilepsy [10].

In this course, the generally accepted ILAE classifications of the term "seizure," referring to a specific neurologic event, will be used. Although the terminology and concepts used to describe seizures and epilepsies have changed, the existing classification of epilepsy syndromes remains essentially the same [8].

Although the classification chart is in column form, it is not hierarchical; levels can be skipped. Seizure classification begins with determining whether the initial manifestations are focal or generalized. If the onset is missed or obscured, the seizure is classified of unknown onset [9]. The 2017 classification scheme allows for appending a limited number of qualifiers to seizures of unknown onset.

The terminology for seizure types is designed to be useful for communicating key characteristics of seizures (***Table 2***). The basic framework of seizure classification in use since 1981 is maintained [9].

In some instances, ancillary information (e.g., electroencephalography, imaging, laboratory studies) is needed to properly classify the seizure [10].

ILAE 2017 CLASSIFICATION OF SEIZURE TYPES			
Focal Onset		**Generalized Onset**	**Unknown Onset**
Basic Version			
Aware	Impaired awareness	Motor • Tonic-clonic • Other motor Nonmotor (absence)	Motor • Tonic-clonic • Other motor Nonmotor
Motor onset Nonmotor onset		–	Unclassified[a]
Focal to bilateral tonic-clonic		–	–
Expanded Version			
Aware	Impaired awareness	Motor • Tonic-clonic • Clonic • Tonic • Myoclonic • Myoclonic-tonic-clonic • Myoclonic-atonic • Atonic • Epileptic spasms Nonmotor (absence) • Typical • Atypical • Myoclonic • Eyelid myoclonia	Motor • Tonic-clonic • Epileptic spasms Nonmotor • Behavior arrest
Motor onset • Automatisms • Atonic[b] • Clonic • Epileptic spasms[b] • Hyperkinetic • Myoclonic • Tonic Nonmotor onset • Autonomic • Behavior arrest • Cognitive • Emotional • Sensory		–	Unclassified[a]
Focal to bilateral tonic-clonic		–	–
[a]Due to inadequate information or inability to place in other categories. [b]Degree of awareness usually not specified.			
Source: [9]			*Table 1*

Epilepsy Classification and Terminology

The terms "generalized" and "focal" have also been applied to the epilepsy syndromes; however, in the 2010 ILAE update, these terms have been abandoned in order to "separate the manifestations from the underlying pathology that produced them" [8]. It is now recommended that each case be characterized according to the large number of other individual features used to diagnose a specific epilepsy syndrome. There are four general groupings of epilepsies: electroclinical syndromes, distinctive constellations/surgical syndromes, nonsyndromic epilepsies (attributed to and organized by structural-metabolic causes), and epilepsies of unknown cause [8].

CHECKLIST FOR CLASSIFYING SEIZURES[a]
Focal Onset
If focal onset, choose one or leave blank if unknown. Aware Impaired awareness (at any time during seizure) *If focal onset, choose Motor, Nonmotor, or Focal to Bilateral Tonic-Clonic. If unknown, leave blank.* Motor • Automatisms • Atonic • Clonic • Epileptic spasms • Hyperkinetic • Myoclonic • Tonic Nonmotor • Autonomic • Behavior arrest • Cognitive • Emotional • Sensory Focal to Bilateral Tonic-Clonic
Generalized Onset
If generalized onset, choose Motor or Nonmotor or leave blank if unknown. Motor • Tonic-clonic • Clonic • Tonic • Myoclonic • Myoclonic-tonic-clonic • Myoclonic-atonic • Atonic • Epileptic spasms Nonmotor (absence) • Typical • Atypical • Myoclonic • Eyelid myoclonia
Unknown Onset
If unknown onset, choose Motor or Nonmotor or leave blank if unknown. Motor • Tonic-clonic • Epileptic spasms Nonmotor • Behavior arrest
Unclassified
[a]Classify by the first sign or symptom.
Source: [10] *Table 2*

The primary goals of the 2010 update of the classification and terminology of epilepsies are to establish standards of practice that will assist with the creation of the most specific and individually tailored treatment plan for each patient, and to help guide research away from generalizations [8]. For example, historically, many structural/metabolic types of epilepsy have been grouped together as "symptomatic focal epilepsies" and differentiated by location of the focus. However, current understanding of epilepsies indicates that location is not the most important factor for the treatment and prognosis [8].

Rather than a diagnosis focused on location (e.g., "symptomatic temporal lobe epilepsy"), diagnosis should reflect important diagnostic features, such as seizure type, lesion type, localization (e.g., "epilepsy with focal seizures secondary to cortical dysplasia in the temporal lobe"), and possibly other factors, including age at onset, electroencephalogram (EEG) patterns, or other features. Because each syndrome/disease type is highly unique, it is hoped that epilepsy research will benefit from the 2010 changes in ILAE classification and terminology and that a better understanding of inadequately differentiated and poorly described seizure disorders/epilepsies may be fostered.

INCIDENCE

Epilepsy is the fourth most common neurologic disorder in the United States, after migraine, stroke, and Alzheimer disease [11; 12]. Active epilepsy affects 3 million American adults, or approximately 1.2% of the U.S. population, and nearly 470,000 children (0 to 17 years of age) [13; 14; 15]. However, the incidence of active epilepsy is 1.9% among adults with annual family incomes less than $34,999 and 0.2% among adults with annual family incomes greater than $100,000. An estimated 150,000 new cases of epilepsy are diagnosed in the United States each year [12; 16].

One in 100 individuals will be diagnosed with epilepsy before 20 years of age [11]. By 75 years of age, roughly 2% of individuals will have active epilepsy and 7% to 10% will have experienced a seizure. New cases of the disorder are most common in individuals younger than 1 year of age and older than 55 years of age, largely because risk factors are highest in these age-groups [14]. In infants, birth injuries, high fevers, temporary metabolic abnormalities (e.g., abnormal blood sugar levels), brain disorders, and congenital defects are the primary causes of epilepsy. From 2 to 20 years of age, the cause is often unknown. After 25 years of age, brain tumors, other structural lesions, and alcohol withdrawal are the foremost contributing causes; however, in about half of this population, the cause is unknown [4]. Stroke is the cause of 50% of all seizures and 30% to 50% of epilepsy in elderly adults [17].

Epilepsy is more likely to occur in certain populations, and there does appear to be some genetic influence. High-risk populations include [12]:

- Individuals who have had a single, unprovoked seizure
- Patients with Alzheimer disease
- Patients with stroke
- Children with intellectual disability
- Children with cerebral palsy
- Children of parents with epilepsy

FINANCIAL IMPACT

The financial issues associated with the care of patients with epilepsy are far reaching. Considerations include reduced income due to the loss of work and increased long-term medical expenses. The direct annual medical care costs of epilepsy in the United States are estimated to be $18.5 billion to $25 billion [18]. Medical costs include office visits, medications, and diagnostic studies. Findings from studies, presented to the American Academy of Neurology (AAN), have indicated that expenses related to other health issues (i.e., excluding epilepsy) in patients with epilepsy accounted for 80% of total annual costs for epilepsy patients [19]. Of that, 13% were attributable to mental health-related expenditures. Outpatient services accounted for 34%, inpatient services for 28%, and drugs for 27% of direct annual costs [19].

Indirect costs include the corresponding reduction in earnings from unemployment and underemployment. Epilepsy is somewhat unique in that 85% of total annual costs (direct and indirect) are productivity-related; these indirect costs are as high as $140 billion per year [18; 20]. It can be a challenge for persons with epilepsy to find employment. In order to work, some patients are forced to accept positions that do not fully utilize their knowledge, skills, and abilities. Although the person with epilepsy may be a good employee and complete assigned tasks, overcoming negative attitudes may be the more daunting challenge. Advocacy efforts have begun to increase the employment and success rates for people with epilepsy in the workplace.

The Americans with Disabilities Act (ADA) was enacted to prohibit disability-based discrimination. Many provisions of the ADA have particular impact on people with epilepsy, including inclusion for safety-sensitive jobs and reasonable accommodation. While many people with epilepsy are able to maintain regular employment without interruption, others may need to miss work because of seizures or changes in medication or to visit a doctor for regular monitoring. Federal laws, including the ADA and the Family and Medical Leave Act, as well as some state laws, offer employment-related protection for individuals with epilepsy [21].

The patient may require referrals to a social worker or state agency for financial support or assistance with living arrangements. These agencies may assist with job training, vocational rehabilitation, counseling, transportation, or housing. Some patients may qualify for financial support through a disability program. For example, the Ticket to Work and Work Incentives Improvement Act of 1999 was established to allow individuals with epilepsy and other disabilities to obtain employment and receive extended Medicare benefits [22]. Additional assistance may be obtained for patients through their local health departments and organizations such as the Epilepsy Foundation.

ETIOLOGY OF SEIZURES

There are many possible etiologies that may lead to the development of seizures or the specific diagnosis of epilepsy. Epileptic seizures have three basic underlying causes: genetic, structural/metabolic, and unknown. For up to half of people with epilepsy, a cause is not known [3; 8]. Some cases of epilepsy are of a genetic origin, but other forms of epilepsy are caused by structural or metabolic defects, which themselves may or may not have a genetic origin [8; 23]. Other cases of epilepsy do not have any identifiable cause. Similar to structural/metabolic defects, the unidentified causes may have a heritable component.

A specific pattern of inheritance of epileptic seizures within the family cannot always be determined. There appears to be a slightly increased risk of epilepsy in close relatives of individuals with seizure disorder compared to the risk in the general population [3; 24]. There is a genetic predisposition for controlling neural inhibition, excitatory neurotransmitters, and neuronal networks involved in the spread of a seizure that suggests a similar predisposition for epilepsy in general.

There is no consistent pathologic identification; however, theories have suggested an alteration due to synaptic structures or deranged chemical neurotransmitters. Researchers have identified a number of gene mutations that may be associated with epilepsy, including *SCN1A* mutation [2; 3; 25; 26]. The genetic link may affect an individual's predisposition to epilepsy or lower the threshold for seizure activity. These individual differences may account for diverse neurologic manifestations after a head injury, fever, or similar insult. Although a hereditary component of the susceptibility to epilepsy has been suspected for many years, many questions remain about the etiologies of epilepsy, the many different genetic factors involved, and the degree of interaction between genetic, metabolic, and environmental factors [24; 27].

Congenital abnormalities, birth injuries, infections, genetic alterations, and hyperpyrexia can result in seizures in the susceptible individual. Even events that occur in the prenatal period may contribute to the predisposition for seizure activity in newborns. For example, infection or systemic maternal illnesses during pregnancy may adversely affect the developing fetus [28]. The fetus is susceptible to CNS injury during gestation. During the perinatal period, the fetus may experience hypoxic and traumatic insults. Adverse situations that occur during the prenatal and perinatal period are believed to be predisposing factors for hippocampal sclerosis in the medial temporal lobe, elevating the risk of seizures [1; 3]. Women are also increasingly in danger of seizures as pregnancy progresses, particularly as related to eclampsia, with hypertension and seizure activity.

Eclampsia is more common among first-time mothers, young mothers, women with pre-existing vascular or thrombophilic diseases, and women whose mother or sister had the condition [3].

A frequent etiology of seizure activity is a head injury. Head trauma has many origins, including motor vehicle accidents, sports-related injuries, and gunshot wounds. A blow to the head resulting in seizures may occur from physical abuse or a fall/accident in the home or it may be work related. Severe injuries, such as trauma with a depressed skull fracture or hematoma, present a greater risk of developing seizures or epilepsy [3; 14; 29]. Traumatic head injury patients have a significantly greater probability than the general population to suffer a seizure during the first year after the injury. A seizure disorder may develop up to four years after a severe head injury [29].

Seizures may also be a symptom of other neurologic disorders and may lead to the diagnosis of a separate disease process. Cerebral vascular disease and arteriosclerotic disease, which deprive the brain of oxygen, may be antecedent to the development of seizures. Arteriovenous malformations, intracranial tumors, and brain abscesses are other CNS lesions that may provoke seizures. CNS infections, such as meningitis, encephalitis, mumps, measles, and diphtheria, may result in seizure activity [4; 28]. Another predisposing factor to the development of seizures is a history of surgical procedures or manipulations of brain tissue. Certain neurologic diseases, such as Alzheimer disease, alter brain structure, and seizures may result from these changes [3].

An uncommon neurologic disease, tuberous sclerosis (TS), is a genetic disorder that results in the formation of benign tumors in vital organs. The tumors may appear in multiple locations, including the brain, heart, and kidneys. The incidence of TS is approximately 1 in 10,000 in the United States [30]. Seizures are a common symptom of this disorder and affect more than 80% of TS patients [31]. Seizure types vary with TS and may present as epileptic spasms, tonic-clonic, atonic, tonic, myoclonic, atypical absence, or focal seizures.

Another common etiology for the development of secondary seizure activity is metabolic change and metabolic disorders. Alterations in electrolyte and glucose availability may enhance the predisposition for seizure activity. Prevalent metabolic changes include hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, and hypocalcemia [32]. Absolute values from the clinical laboratory are not always predictive of seizure activity because rapid metabolic shifts can predispose neurologic tissue to electrical instability. Other metabolic changes include those associated with organ dysfunction, including uremic and hepatic encephalopathy. Hypertensive encephalopathy may result in convulsions. In these cases, the blood pressure is generally greater than 250/150 mm Hg [33]. Other metabolic disorders that may predispose individuals to seizures include phenylketonuria, Niemann-Pick disease, Gaucher disease, mucopolysaccharidosis, and hepatic porphyria [32].

Exposure to toxins is an additional etiology for the development of seizure events. Toxins, including lead, carbon monoxide, and pesticides (e.g., organophosphates, carbamates), have been implicated in the development of seizure activity. Prescription medications, including antibiotics, psychotropic agents, antiarrhythmic agents, anesthetics, barbiturates, and benzodiazepines, are known causes of seizures in susceptible individuals [34]. Radiographic contrast agents are another occasional causative factor. Drugs of abuse, such as alcohol, cocaine, amphetamines, barbiturates, and benzodiazepines, are known causative agents for the development of seizures, especially when associated with overdose and withdrawal [35].

One evening in Japan in 1997, 685 people simultaneously developed epileptic seizures. Most were children watching a televised cartoon with a background of rapidly changing blue and red. Although this situation was unprecedented, rapidly changing color patterns may cause nerve cells to be stimulated more quickly, resulting in seizure activity. This is referred to as photosensitive epilepsy [36]. The researchers who reported this incident proposed the term "chromatic sensitive epilepsy" [37].

AGE AND ETIOLOGY

The age at which a patient first develops the seizure is often an indication of the etiology, if an identifiable etiology can be elicited. Neonates and infants often experience seizures due to perinatal injuries, hypoxia, metabolic changes, and congenital defects. Children may experience seizures due to hyperpyrexia, CNS infections, or idiopathic reasons; a primary cause of seizures is head trauma [11; 24]. In adulthood, a brain mass is a common etiology. Cerebrovascular disease is the most common cause in the elderly [38; 39].

BASIC PATHOPHYSIOLOGY OF SEIZURES

The mechanism of cerebral function during seizures is very complicated and the object of study by many investigators and to date is not fully understood. The brain has even been studied in vitro to help elucidate the nature of epileptic activity [40]. This section will provide a very basic and brief description of the approximate physiologic process during a seizure.

It is well understood that the brain transmits information and controls movement by electrical and chemical processes. Neurons located in the cerebral cortex intercommunicate to allow the integration of higher mental function as well as the required coordination for normal motor activity. Any event that significantly disrupts the normal propagation of this activity may result in a seizure.

The neuronal membranes and synapses are permeable and can be influenced and/or activated by many factors, including glucose and electrolyte levels, ischemia, trauma, and temperature [4]. Some cells, such as neurons in the temporal lobe, are more easily excitable than others. When there is significant cerebral malfunction, the affected neurons can become an epileptogenic focus and begin to discharge rapidly. The involved cells may start firing with an increased frequency and with increasing amplitude. If this process continues without inhibition, the nearby neurons may be recruited and the process can begin to spread. The excitation may involve the local area, or it may spread to the entire cerebral cortex [3; 41]. The thalamus, basal ganglia, and the brainstem can be affected. If the brainstem is involved, there may be total loss of consciousness.

There are inhibitory neurons present that can act, in conjunction with exhaustion of the excitatory neurons, to end the seizure. The activity of the inhibitory neurons may be enhanced by some of the antiepileptic medications [3]. When the seizure, or ictal, activity ends, there may still be inhibition of the CNS, leading to depression, impairment of consciousness, and somnolence.

As mentioned, seizure activity can originate in an area of the brain that contains an abnormality, such as gliosis or scar tissue. These regions of altered tissue can interfere with normal neuronal activity in a way that predisposes them to initiate seizures and become an epileptogenic focus. These foci of seizure activity can be located in any of several locations in the brain.

Animal studies have shown that with repetitive seizure activity, the likelihood of additional seizures becomes greater. To patients, this means that early and appropriate intervention is necessary to obtain the best seizure control [40; 41; 42].

PHASES OF A SEIZURE

The three generally recognized phases of a seizure are the prodrome (or preictal), ictal, and postictal stages [43]. Not all patients experience, nor do all seizures include, every phase. The prodromal phase can last several days preceding a seizure. The prodrome is generally characterized as malaise or emotional changes [43]. An aura occurs immediately prior to a seizure, usually lasting a few seconds. Patients often describe an aura as a warning. An aura may be autonomic or it may involve the auditory, olfactory, sensory, or visual senses. The description of an aura can vary and may include weakness, an epigastric sensation, a sense of fear, visual hallucinations, aphasia, headache, feelings of being hot or cold, or

sensing unpleasant odors [43]. If a patient experiences auras (and not all do), the auras are usually fairly consistent in that individual. However, auras may vary in the same patient, and the use of antiepileptic drugs (AEDs) may alter or obscure the aura.

The ictal phase is the duration of the actual seizure activity [43]. The patient experiences a paroxysmal, uncontrolled, abnormal, and excessive discharge of electrical activity in the brain [43]. There are also corresponding EEG changes [41]. The clinical manifestations will coincide with the type of seizure activity that the patient is experiencing.

The postictal period is the interval after the seizure episode. The patient may experience some change in consciousness or behavior [43]. Some patients experience Todd paralysis, a numbness or weakness of an affected extremity or the side of the face. After a tonic-clonic seizure, the postictal phenomena may be more severe. The patient may experience amnesia, confusion, fatigue, and/or coma [41]. Often, neuronal discharges remain abnormal and the EEG may indicate some slowing.

A fourth phase recognized by some experts is the interictal phase, the period between seizures. Many people with epilepsy suffer from emotional changes during this phase, including fear, anxiety, and depression [44]. These disturbances can be more troublesome to patients than the seizures themselves.

EXACERBATING FACTORS

There are several known conditions that may cause an increase in seizure activity in susceptible individuals. Sleep deprivation, mental and physical stress, acute illness, excessive fatigue, flashing lights, and hyperventilation are among the most common exacerbating factors [3; 45]. The use or abuse of stimulants or alcohol also has been linked to the increase in seizure activity in sensitive individuals.

CLASSIFICATION OF SEIZURE

Seizures are broadly classified according to whether they originate in bilateral cortical networks (generalized onset) or networks limited to one hemisphere (focal onset). The classification of a patient's seizure first by type of onset is meaningful for a number of reasons. Classification provides a common terminology and understanding, directs effective treatment, influences appropriate management and prognosis, and guides patient education [2; 10]. It is important to note that the descriptors focal and generalized are not representative of lesion location, as focal lesions can cause both generalized and focal seizures [8].

The major classifications of seizures are not based upon severity or loss of consciousness but are determined by the location of the initiation of the seizure. Although it is possible to have both generalized and focal seizures, the combination is extremely rare. By far, the greatest numbers of patients experience either focal onset or generalized onset seizures.

CHANGES IN SEIZURE TYPE CLASSIFICATION

Following are the changes in seizure type classification from 1981 to 2017. Several of these changes were already incorporated into the 2010 revision of terminology [9]:

- "Partial" was changed to "focal" globally.
- Certain seizure types can be either of focal, generalized, or unknown onset.
- Seizures of unknown onset may have features that can still be classified.
- Awareness is used as a classifier of focal seizures.
- The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized were eliminated.

- New focal seizure types include automatisms, autonomic, behavior arrest, cognitive, emotional, hyperkinetic, sensory, and focal to bilateral tonic-clonic seizures. Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be either focal or generalized.
- New generalized seizure types include absence with eyelid myoclonia, myoclonic absence, myoclonic-tonic-clonic, myoclonic-atonic, and epileptic spasms.

GENERALIZED SEIZURES

Generalized seizures begin and spread rapidly in bilaterally distributed networks and are followed by a period of postictal phase of continued altered consciousness [8; 46]. They are thought to originate from structures deep within the brain, radiating outward to the cortical surface. The networks may include cortical and subcortical structures, but the entire cortex is not necessarily affected. When a generalized seizure begins, there is synchronous involvement of the entire brain with diffuse EEG abnormalities. Approximately 20% to 25% of seizures are classified as generalized at onset [41]. Generalized seizures may result in a loss of consciousness, convulsions, falls, or muscle spasms. Some generalized seizures may encompass all of these events, while others may involve only one symptom.

Generalized-onset seizures can be further classified as motor- and nonmotor-onset. Motor-onset seizures include tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, and epileptic spasms. Nonmotor-onset (absence) seizures include typical absence, atypical absence, myoclonic absence, or absence with eyelid myoclonia. Level of awareness is not used as a classifier for generalized seizures, since the large majority are associated with impaired awareness [10]. Each of these seizures occurs with a predictable pattern accompanied by distinctive differences based on the individual patient.

Absence Seizures

Historically known as petit mal seizures, absence seizures are rare in adulthood but more common in children [44]. They are characterized by a brief period of altered consciousness, often described as a staring spell. There are four recognized types of absence seizures—typical, atypical, myoclonic, and eyelid myoclonia [9].

The typical absence seizure is the most common type and is associated with little to no cognitive impairment. The duration of the seizure is generally 5 to 30 seconds. The absence seizure may occur up to 100 times per day or only rarely [10; 41]. The patient is often described as having a blank stare that interrupts motor and mental activity, which begins and ends suddenly. No loss of postural tone occurs, but a mild increase or decrease in muscular tone may be experienced. Occasionally, the patient will exhibit minimal myoclonic movements around the eyelids or mouth. Automatisms associated with the seizure, including chewing or rapid blinking, may occur. During the seizure there is a loss of awareness [44]. Usually, the patient will be unresponsive when spoken to [10]. There is usually no postictal period, and the individual may continue activities with full awareness after the seizure has subsided.

The EEG pattern is unique and probably related to an etiology that is different than other seizure types. The typical absence seizure ictal EEG shows a characteristic three-per-second generalized spike-and-wave discharge [9]. Absence events may often be elicited with hyperventilation.

Atypical absence seizures are less common than typical absence seizures. The characteristic blank stare/consciousness shift is similar in both types, but atypical seizures have several distinct features and are associated with severe neurologic impairment and a poorer prognosis (i.e., significantly abnormal cognitive and neurodevelopmental outcomes) [47].

Changes in tone are more pronounced than in typical absence seizure [10]. The ictal phase may be longer and more pronounced motor symptoms may occur. Although there is a loss of awareness, many patients exhibit some degree of responsiveness to the surroundings during the atypical seizure [48]. Voluntary behavior is not uncommon. A pathophysiologic distinction is that typical absence seizure activity involves only thalamocortical circuits whereas atypical seizures also involve limbic circuitry [47]. The frequency of the EEG spike-and-wave discharge also differs from that of typical absence seizure activity [10]. The ILAE retained the distinction between typical and atypical absence seizures, because the two types usually are associated with different EEG findings, epilepsy syndromes, therapies, and prognoses [10].

Eyelid myoclonia are myoclonic jerks of the eyelids and upward deviation of the eyelids during an absence seizure. There may or may not be a brief loss of awareness. Eyelid myoclonia can be difficult to categorize [10].

Some children who experience absence seizures also have associated tonic-clonic seizures [24]. Most children will outgrow typical absence seizures and have no sequelae; however, individuals who experience atypical absence seizures in childhood are more susceptible to developing tonic-clonic or focal seizures in adulthood. It is known that seizures cause excitotoxic cell death, and it is believed that mechanisms responsible for atypical seizures also cause neural hyperexcitability and reduced inhibition in proximal structures, leading to recruitment and paroxysmal seizure activity/propagation into previously uninvolved areas of the brain [47].

Tonic-Clonic, Tonic, and Clonic Seizures

The seizure type focal to bilateral tonic-clonic is in a special category because of its common occurrence and importance, even though it reflects a propagation pattern of seizure activity rather than a unique seizure type. The phrase focal to bilateral tonic-clonic replaces the older term secondarily generalized tonic-clonic. In the new classification, bilateral is used to describe propagation patterns of seizures and generalized is used for seizures of generalized onset [10].

A tonic-clonic seizure has historically been referred to as a grand mal seizure. Tonic-clonic seizures account for only about 20% to 25% of all seizures [41]. However, when most individuals envision a typical seizure, the events of a tonic-clonic seizure are considered the classic occurrence [3]. At the onset of the seizure, the patient will often vocalize a sudden cry. The cry is caused by the abrupt contraction of the diaphragm and chest muscles with the subsequent expulsion of air through the respiratory tract [41]. This is quickly followed by the tonic phase. It may be observed as a fall with a stiff or rigid posture. The eyes often roll back; the jaw is clenched, and the muscles are contracted. The patient may bite his or her tongue or cheek during this stage. The tonic phase will last approximately 30 to 60 seconds. Clonic movements will follow this phase with repetitive flexion movements of the body, including the arms, neck, and hips. The movements are rhythmic, synchronous, and jerky. The clonic movements usually continue for five minutes or less. The patient may produce excessive saliva, exhibit shallow breathing, or develop cyanosis. The clonic movements will progressively slow, then stop. The patient will then become flaccid and exhausted. Anal and urinary sphincters may relax, with resulting incontinence. The patient may remain unconscious for several minutes. As consciousness returns, the patient often experiences fatigue, loss of memory, headache, and confusion. This postictal period can last from several minutes to hours [41;44].

Tonic-clonic seizures can occur in an unpredictable pattern and vary in frequency. A patient may experience a pure tonic seizure without clonic findings or a pure clonic seizure without the associated tonic events. These events are less common and are generally associated with other seizure types.

Myoclonic Seizures

A myoclonic seizure causes a quick muscular jerky movement. This movement may affect a specific part of the body, such as the face, trunk, or extremities, or it may involve the entire body. A myoclonic seizure results in the involuntary, momentary, total loss of major muscle movement or muscle tone. These movements can be as simple as a jerky contraction or a head that droops, or as overwhelming as the entire body collapsing. Consciousness is briefly impaired. The jerky movements can be quite violent and cause the individual to fall or hit objects. Myoclonic seizures may occur as single events or be repeated in a rapid fashion [10; 44]. Myoclonic-atonic was previously called myoclonic-astatic. Seizures with this characteristic are common in juvenile myoclonic epilepsy (JME) [10].

Atonic Seizures

An atonic seizure or "drop attack" is evidenced by a seizure in which a patient suddenly collapses and/or falls, with the legs unable to support the body, or if seated, slumps and/or falls to the floor [3; 44]. The patient is unconscious during the event but will regain consciousness after a short period of approximately 10 to 60 seconds [4; 38; 44]. The postictal period is short, and patients can generally continue with their activities. Less typically, individuals may experience a sudden loss of tone in the muscles of the jaw or neck. These seizures generally begin in childhood, between 2 and 5 years of age, or following widespread traumatic brain injuries in adults [46].

FOCAL SEIZURES

Focal seizures (previously referred to as "partial seizures") are the more common classification and originate in a circumscribed area or areas of the brain (i.e., a localized brain disturbance). This type of seizure occurs in 75% to 80% of patients with epilepsy [44]. Focal-onset seizures vary in terms of manifestations and severity and can result in changes in motor, sensory, and emotional functions, with or without impairment of consciousness. Focal seizures are further described according to symptoms and brain involvement [8]. Focal seizures should be classified by the earliest prominent feature (with the exception of a focal behavior arrest seizure) [10].

For focal-onset seizures, specification of the level of awareness is an optional classifier [9]. Retained awareness means that the person is aware of self and environment during the seizure, even if immobile. A "focal aware seizure" (with or without any subsequent classifiers) corresponds to the prior term "simple partial seizure." A "focal impaired awareness seizure" (with or without any subsequent classifiers) corresponds to the prior term "complex partial seizure." Impaired awareness during any part of the seizure renders it a focal impaired awareness seizure [9].

In the past, a focal seizure was considered to be complex if it included the corresponding symptom of impaired awareness or loss of consciousness [38; 44]. However, the words "complex" and "simple" can be misleading in some contexts. Complex implies that this seizure type is more complicated or difficult to understand than other seizure types. Simple seems to trivialize the impact of the seizure to the patient who finds nothing simple in either the manifestations or consequences of the seizure [9]. For these reasons, "complex" and "simple" are discontinued terms in the 2017 ILAE classification scheme [9].

A focal motor seizure occurs from a focus in the region of the brain's motor cortex. Motor activity occurs in the corresponding part of the body innervated by the motor neurons that are affected. The hands and fingers have a large cortical representation; consequently, seizures are frequently noticed in these areas. The duration of these seizures is usually one to two minutes, although the patient may require additional time to completely recover after the event [4; 7]. The patient will present with twitching/jerking movements in an extremity, the face, the eyes, or another area of the body. The patient remains fully conscious and aware of the

seizure but has no control of the event [4]. These seizures usually remain localized, but the involuntary movement may spread centrally and involve an entire limb, one side of the body, or the entire body [4; 10; 44]. A Jacksonian march seizure involves the recruitment of additional muscles along the same side of the body in a progressive, step-wise fashion. The seizure may progress to involve other parts of the brain and affect other parts of the body [4].

Motor-onset focal seizure behaviors include atonic (loss of tone), tonic (sustained stiffening), clonic (rhythmic jerking), myoclonic, or focal flexion/extensions of arms and flexion of trunk (epileptic spasms). Other less obviously focal motor-onset behaviors include automatisms and hyperkinetic activity (e.g., pedaling, thrashing) [10]. Automatisms are more or less coordinated, purposeless, and repetitive motor activity and may be seen in focal seizures and in absence seizures [10]. Some automatisms overlap other motor behaviors, such as hyperkinetic activity, which renders classification ambiguous. The 2017 ILAE classification scheme arbitrarily groups pedaling activity with hyperkinetic seizures rather than with automatism seizures. Hyperkinetic seizures are a new addition to the focal seizure category.

Nonmotor-onset focal seizures can manifest as autonomic, behavior arrest, cognitive, emotional, or sensory dysfunction [10]. Focal autonomic seizure symptoms include those consistent with involvement of the autonomic nervous system, including cardiovascular, gastrointestinal (GI), sudomotor, vasomotor, and thermoregulatory functions (e.g., changes in heart or respiratory rate, increased sweating, or unpleasant sensations in the viscera or head) [3; 10; 49]. Other patients may experience piloerection (goosebumps), pupillary changes, nausea, and flushing.

The dominant feature of a behavior arrest seizure (formerly "akinetic seizure") is the cessation of activity throughout the seizure, including cessation of movement (e.g., freezing, immobilization) and unresponsiveness [10]. Cognitive seizures imply impaired language or other cognitive domains or positive features (e.g., *déjà vu*, hallucinations, illusions, perceptual distortions). Emotional seizures involve anxiety, fear, joy, other emotions, or appearance of affect without subjective emotions [10].

A focal sensory seizure is a perceptual experience not caused by appropriate stimuli in the external environment [10]. It is usually not observable by others but may involve any of the senses [10]. Transient sensory symptoms are experienced and may involve alterations in vision, hearing, taste, touch, and smell. As with motor seizures, there is no loss of consciousness [10]. These sensory seizures may occur in the parietal, occipital, or posterior temporal lobes. The patient may describe paresthesias or numbness, tingling, bright flashing lights in vision fields, nausea, odd smells, buzzing sounds, voices, epigastric sensations, or difficulty speaking [50]. Diagnosis of this type of seizure would include specific descriptors of the sensory involvement (e.g., visual, auditory, olfactory, gustatory, epigastric) or a general descriptor (e.g., illusory experiential seizure), especially with multiple sensory involvement [50].

The events of a focal seizure have been described as follows:

The patient suddenly stopped talking and stared at the ground. Her head moved slowly to the side and she began rubbing the table with one hand, as if she was smoothing down a piece of paper. Her movements were slow and appeared deliberate. I asked the patient to remember "purple elephant." I asked the patient to lift one foot off of the floor, but there was no response. The event lasted 90 seconds. The patient moved back to her previous position in the chair with her head in a neutral position and her hand in her lap. She looked at me, with a groggy expression, and stated repeatedly, "I'm ok." The patient was slow to respond and lethargic for several minutes. After she was alert, she could not recall the event or the phrase "purple elephant." The patient complained of a headache and fatigue. After a period of rest, she was able to resume her usual activities.

EPILEPTIC SPASMS

Epileptic spasms are characterized by sudden flexion, extension, or mixed extension/flexion of mainly proximal and truncal muscles that is usually not so sustained as a tonic seizure but more sustained than a myoclonic movement, lasting approximately one second [49]. Epileptic spasms may occur in other forms, such as grimacing or head nodding, and they frequently occur in clusters. Spasms are most commonly observed in infants and young children, and this classification replaces the previous category of infantile spasms [10].

UNCLASSIFIED SEIZURES

Unclassified seizures include both seizures with patterns that do not fit into the other categories or seizures presenting insufficient information to allow categorization. This classification is reserved for unusual events likely to be seizures but not otherwise characterized. If the seizure is unclassified because the type of onset is unknown, a limited classification may still derive from observed features [10].

THE EPILEPTIC SYNDROMES

There is a difference between the classification of seizure types and epileptic syndromes. Some patients with epilepsy experience one type of seizure; others experience several different seizure events. Different syndromes account for the varying patient histories, etiology of seizures, seizure type, clinical presentation, EEG readings, and neuroimaging findings. The ILAE has established an International Classification of Epilepsies and Epileptic Syndromes. The Classification was updated in a 2017 position paper to reflect the gain in understanding of the epilepsies and their underlying mechanisms. The updated epilepsies classification scheme is designed to work with the ILAE's 2017 revised seizure classification scheme [9; 51]. In the 2017 epilepsies classification paper, the term "benign" is replaced by the terms "self-limited" and "pharmacoresponsive;" the term "developmental and epileptic encephalopathy" can be applied in whole or in part, where appropriate [51].

The ILAE Task Force defines an epilepsy syndrome as "a characteristic cluster of clinical and EEG features, often supported by specific etiological finds (i.e., structural, genetic, metabolic, immune, and infectious)" [51]. At its core, an epilepsy syndrome must have characteristic electroclinical features [51]. Syndromes often have age-dependent presentations and may also remit at certain ages. Accordingly, the ILAE position papers separately describe syndromes with onset in neonates and infants (up to 2 years of age), syndromes with onset in childhood, and syndromes that may begin at variable ages (meaning in both pediatric and adult patients). A separate position paper on idiopathic generalized epilepsies also is available [52]. Many syndromes are strongly correlated with a range of specific intellectual, psychiatric, and other comorbidities [51].

The syndromes are further subdivided into generalized, focal, or generalized and focal, based on seizure type(s), with a separate category for syndromes with developmental and epileptic encephalopathy (DEE) or progressive neurological deterioration [53]. The term DEE denotes an epilepsy associated with developmental impairment that may be due to both the underlying etiology and superimposed epileptic activity. Most DEEs present very early in life [53].

The 2017 epilepsies classification presents three levels of diagnosis. Where possible, a diagnosis at all three levels should be sought [51]. The first level of diagnosis is seizure type: focal, generalized, or unknown onset. In settings without access to EEG, video, and imaging studies, seizure type classification may be the maximum diagnostic level possible [51]. The second level of diagnosis is epilepsy type: focal, generalized, or unknown onset and a new category of "combined generalized and focal epilepsy." Many epilepsies will include multiple seizure types [51]. The third level of diagnosis is epilepsy syndrome—a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together [51].

Common epileptic syndromes include febrile epilepsy, childhood absence epilepsy, JME, and reflex epilepsies [54]. In total, the ILAE has identified more than 30 epileptic syndromes [54].

DIAGNOSING SEIZURE DISORDERS

PATIENT HISTORY

The patient's history and the witnesses' detailed account of the seizure are critical elements in treating any patient with epilepsy [4]. These reports are often the primary mechanism to assess seizure intensity, duration, and frequency. An accurate and detailed seizure description is only achieved by asking open and pertinent questions. A seizure diary, kept by the patient and/or his or her family, can provide very useful information.

The patient should be questioned regarding any significant medical history [4; 55; 56]:

- Has the patient ever experienced head trauma, loss of consciousness, CNS infection, or febrile seizure?
- Is there any history of accident, injury, or hospitalization?
- Is there any significant childhood illness or history, such as a perinatal insult or altered developmental history?

The patient should also be questioned regarding any significant family history of epilepsy. In addition [4; 56]:

- Determine if the patient has ever had a prolonged seizure in the past that would be considered severe or suggest status epilepticus.
- Ask which medications were used in the past and which drugs are currently prescribed.
- Find out if there are any known allergies.
- Ascertain the response to past medications and compliance with the prescribed regimen.
- Recognize that important aspects of the patient's medical treatment will involve the past surgical history, psychiatric history, previous diagnostic testing, and social history.
- Investigate social history, including the patient's educational achievement, employment, and living arrangements.
- Obtain information regarding the use of tobacco, caffeine, alcohol, illicit drugs, and other substances.
- Inquire about the patient's sleep patterns, methods of transportation, and leisure activities.

Determining the patient's knowledge of the seizure is an important aspect of the history [4; 55; 56]:

- Can the patient and/or family describe the seizure episode?
- Are there any aggravating or precipitating factors, such as flashing lights or sleep deprivation, which correspond to the event?
- What occurs during the preictal, ictal, and postictal periods?
- How does the patient first gain knowledge that a seizure has occurred or is going to occur?
- The earliest emotional or sensory symptoms experienced by the patient may often convey very accurate localizing information.

The patient and family/witness should be questioned about the duration of the seizure, timing the active event in seconds [4; 56]:

- Is there any change in consciousness?
- Is the patient able to react, recall, or respond in a meaningful way?
- Can the patient follow commands, such as clapping hands, or remember something unusual, such as "green cat?"
- Can the patient answer a question during the seizure?
- What forms of motor activity occur?
- How does the patient tolerate the seizure?
- Are there any associated symptoms, such as incontinence, respiratory changes, or injuries?
- How does the patient feel during the postictal period?

Any witness can provide substantial information regarding a seizure episode. The witness can describe the patient's level of consciousness and behavior. Furthermore, the witness can detail events related to the patient's muscle tone, injuries, state of confusion, residual paralysis, and alertness [4; 56]. Fortunately, another individual often accompanies the patient with epilepsy due to imposed driving restrictions.

The patient's and/or witness's report of seizure activity is significant in caring for the person with epilepsy. These reports are often the primary mechanism to assess seizure intensity, duration, and frequency. This information often determines medication choices, dosage adjustments, and follow-up recommendations.

Patients and family members often inaccurately label the type of seizure experienced. Healthcare personnel should interpret a patient's description of the seizure in order to determine seizure type. Patients may state that they have "grand mals" when the seizures are actually tonic-clonic or focal seizures, including focal seizures that evolve bilaterally. Or, a patient may simplify the categorizations to "little" and "big," describing different manifestations of focal seizures. Often, patients have referred to their seizures with their individual terminology for years and renaming them is not helpful. A notation can be placed in the chart clarifying the patient's descriptions to assist all care providers to depict the seizures in a consistent and accurate manner.

A study conducted to determine seizure reporting to general practitioners has revealed that patients reported significantly more seizures on questionnaires completed anonymously, after visits to their doctors, than they reported during the office visits [57]. Patients may conceal seizure reporting because of the effect on various lifestyle patterns, including driving, employment, and leisure activity.

Patients and families should be encouraged to provide accurate and honest answers. A supportive environment should be provided to allow for candid and truthful discussions in order to provide the most applicable and beneficial care.

PHYSICAL EXAMINATION

A comprehensive physical examination helps to determine the patient's health status, contributing factors, or secondary causes of epilepsy. The assessment should focus upon genetic diseases, neoplasms, infections, poisonings, and autoimmune diseases, including systemic lupus erythematosus. Characteristics of organ dysfunction, including hepatic, cardiac, pulmonary, and renal alterations, should also be evaluated. A general physical examination should be performed to exclude a non-neurologic cause of the seizure [56].

Neurologic Examination

A comprehensive neurologic evaluation is essential for any individual who has experienced a seizure or has a diagnosis of epilepsy. Seizures may be the result of a distinct neurologic disorder or the disorder may be epilepsy itself. The neurologic examination should be directed at finding clinical evidence of a focal brain lesion [56].

The patient's mental status is evaluated throughout the examination. Mental status evaluation includes an assessment of orientation and level of alertness, affect, and memory. Speech is evaluated for articulation, fluency, comprehension, and repetition. The patient's cognitive function is assessed for attention, memory, information, calculation, and abstract thinking [3; 58].

The patient's neck should be evaluated for suppleness and carotid artery bruits. Cranial nerves I through XII are individually assessed and evaluated [59]. This assessment includes an examination of the eyes, including vision, eye movements, extraocular movements, pupil equality and reaction to light, and accommodation, fundi, and visual fields. The cranial nerve examination includes an assessment of smell, jaw clenching, facial symmetry, facial sensation, taste, hearing, speech, tongue and uvula position, gag reflex, and trapezius/sternomastoid movement [60].

An evaluation of the motor system is performed to determine muscular function. Strength is appraised in upper and lower extremities on a five-point scale. Muscles are assessed for tone and bulk. Involuntary movements, such as tremor, clonus, and fasciculations, are noted. The patient will be asked to perform rapid alternating movements, pointing movements, pronator drift, and the Romberg test, as well as other tests to assess coordination. The patient's gait should also be assessed, including posture, base, and tandem walking. Sensations are tested in all extremities and include the ability to sense pinprick, body part position, light touch, temperature, and vibration [60].

Reflexes are evaluated and deep tendon reflexes are examined in all extremities, including the biceps, triceps, quadriceps, hamstrings, and the muscles affecting the knees and ankles. Additional reflexes are assessed, including those of the abdomen, feet, and genital area [60]. In the acute care setting, additional neurologic testing is appropriate. A detailed assessment will include the Glasgow Coma Scale and measures of level of consciousness in association with stimuli [60].

Epilepsy is unlike many diseases in which the physical manifestations are the key to the diagnosis and treatment. In fact, the physical exam is often normal and unremarkable when the patient is not experiencing a seizure. Physical findings that are observed may be consistent with epilepsy or with a secondary medical or neurologic disorder. Some of the important clinical findings include alterations in consciousness, sensation, motor abilities, and reflexes [60]. If seizures are due to an underlying disorder, these conditions are often discovered during the physical examination.

DIFFERENTIAL DIAGNOSIS

The diagnosis of epilepsy is based on several factors, with history as one of the most significant. A clinical history of seizures with concurrent EEG changes can usually establish the diagnosis of epilepsy. Signs or symptoms that may be most useful in the differentiation of epileptic seizures from other conditions include abrupt onset; altered or lost awareness (if not a focal seizure variant); brief duration; rapid recovery; and recurrent stereotypic episodes [9]. However, there are numerous disorders that mimic epilepsy. These disorders must be differentiated because they can be serious, life-threatening conditions that require intervention and treatment. Some conditions that must be ruled out in the differential diagnosis include syncope, hyperventilation syndrome, transient ischemic attack (TIA), migraine, and cataplexy [1; 56].

Syncope can occur due to arrhythmia, cardiac disease, vasovagal response, and orthostatic hypotension [60]. Syncope can present with jerking movements and incontinence, which may confuse the diagnosis. Differentiating characteristics in syncope include light-headedness, weakness, hypotension, and nausea. In a simple "vasovagal faint," the person usually recovers immediately after becoming recumbent.

Hyperventilation is often diagnosed in young adults. The patient may exhibit carpopedal spasms or muscle cramping similar to epileptic twitches. The patient, however, will usually complain of shortness of breath with light-headedness [61]. These patients will also exhibit alterations in breathing that are dissimilar to those noted during an epileptic seizure.

TIAs usually present with paralysis, visual changes, aphasia, and sensory alterations. The patient is conscious during a TIA, although confusion may occur. Most symptoms of a TIA disappear within an hour, although they may persist for up to 24 hours [62].

A migraine can occur with an aura, although the aura associated with migraine is generally of a longer duration than a focal seizure. Cataplexy occurs in patients diagnosed with narcolepsy [60]. The sudden changes in movement and muscle tone noted during cataplexy could mimic seizures; however, the other clinical symptoms, including daytime sleep attacks, challenge this diagnosis.

There are other disorders that imitate the clinical picture of a seizure disorder. Metabolic and toxic disorders can occur in a number of settings. These situations include alcoholic blackouts, ingestion of hallucinogens or anticholinergics, sleep disorders, cardiovascular events, porphyria, movement disorders, and psychiatric disorders [63]. Some individuals will have a variety of independent, yet overlapping diagnoses. There may be a pathophysiologic and clinical correlation of migraine, epilepsy, and cerebral vascular disease in the same individual. One diagnosis does not automatically rule out other considerations in the same patient.

Psychogenic Pseudoseizures

Psychogenic pseudoseizures can be difficult to diagnose accurately and often require simultaneous EEG and video monitoring. The patient often relates a history of sexual abuse, post-traumatic stress disorder, or other psychologic trauma [64]. The seizures may appear very similar to an epileptic seizure, but careful history and seizure descriptions are crucial to an accurate diagnosis. Frontal lobe epilepsy is often confused with pseudoepileptic seizures. Pseudoepileptic attacks have no physiologic CNS abnormalities. Injuries are uncommon with pseudoseizures. When eliciting the seizure description from the patient or witness, every detail can be important.

The following is an example of a patient with nonepileptic pseudoseizures:

Patient E is a man who experiences pseudoseizures after serving in the Vietnam War. A witness described the patient's pseudoseizure: "He began by crying, then becoming very withdrawn and quiet. He slowly leaned against the wall and slumped gradually to the floor onto his back. His eyes rolled around and his mouth was moving as if he was speaking without any words. Movements began in his left shoulder then proceeded down his arm, then throughout his entire body. His arms and legs flayed around, as if he were running away from something." Further questioning about the movements of the extremities revealed that the patient's arms moved independently of each other, in a smooth, nonrhythmic fashion. His legs had a kicking and running movement to them.

Although this description does not automatically discount an epileptic seizure, there are some details that are not consistent with a common epileptic seizure. One of the most obvious inconsistencies is that the event does not follow a neuroanatomic pattern. Movements during a pseudoseizure may have personal symbolic significance to the patient.

DIAGNOSTIC STUDIES

There are several diagnostic procedures that aid in the evaluation and management of individuals with suspected seizures or epilepsy. There are procedures available to evaluate brain wave activity, visualize brain structure, and explore the blood flow and function of specific regions of the brain. Each test is meaningful and helpful when applied in appropriate and unique situations. However, EEG and magnetic resonance imaging (MRI) are the primary tests utilized.

Electroencephalogram

The EEG measures the very small electrical signals that are constantly produced throughout the nerve cells of the brain. The brain waves are labeled by their pattern and frequency and described as alpha, beta, delta, and theta rhythms. They normally occur between the range of 2 to 12 cycles per second. The EEG guides the identification and location of seizures and may establish the diagnosis of epilepsy. Unfortunately, it cannot always confirm the diagnosis. Seizures usually occur randomly, and the test may be completed during a time when no seizure activity is present. A small percentage of patients are diagnosed with epilepsy with no EEG changes, while other patients may have EEG abnormalities without epilepsy. Still, the EEG remains one of the most critical tools to assist with the diagnosis and understanding of epilepsy [65; 66].

The most frequently ordered test is a random, routine, or interictal EEG. This is performed when the patient is not having a seizure. As noted, a patient with epilepsy can have abnormal electrical activity in the absence of a seizure. These interictal epileptiform abnormalities may include a spike, which is a burst of electrical activity that is different from the

normal EEG pattern. Spikes may occur in a focal area or in multiple foci throughout the brain. The interictal EEG is a beneficial test because a patient can schedule it at a time that is convenient. Unfortunately, although this is the most agreeable test for all individuals involved, seizures may not be present, and a definitive diagnosis cannot always be obtained [38; 65]. However, a great majority of patients with epilepsy will have interictal EEG changes consistent with epilepsy [38; 66]. Interictal background EEG frequencies that are slower than normal for age usually suggest a symptomatic epilepsy (i.e., epilepsy secondary to brain insult). Normal background suggests primary epilepsy (i.e., idiopathic or possibly genetic epilepsy). Thus, EEG background offers important prognostic and classification information [67].

Some EEG patterns are associated with specific types of seizures. A bilateral 3 Hz spike-wave discharge on the EEG is a classic pattern for a patient with typical absence seizures, especially during hyperventilation [34; 65]. Patients with genetic epilepsies often have a positive response to photic stimulation [66].

Often, an ictal EEG is required in order to provide the most accurate diagnosis and the most beneficial treatment. If the timing happens to be coincidental, a seizure may be captured during a random EEG. Unfortunately, this cannot be predicted and does not generally occur. Various methods are used to capture a seizure event, such as through a sleep-deprived EEG, a 24-hour monitor, or inpatient monitoring. A sleep-deprived EEG requires the patient to remain awake during the usual hours of sleep, prior to the test. Sleep deprivation may result in a higher probability of capturing seizures on the EEG, especially for patients who are susceptible to seizures due to lack of sleep or for patients who experience nocturnal seizures [58; 65]. However, all-night sleep deprivation is inconvenient for the patient and often for the whole family and may induce unwanted seizures, particularly after leaving the EEG department in the awakening period. Patients with JME are particularly vulnerable because seizures mainly occur on awakening after sleep deprivation [66]. Drug-induced sleep has been applied in some EEG departments as a substitute for all-night sleep deprivation. The patient is medicated prior to or during electrode placement, with the aim of obtaining a sleep-stage EEG. However, drugs that induce sleep may interfere with normal patterns. Patients may find it difficult to be sufficiently alert for the rest of the day and may also have a seizure on awakening [66].

A 24-hour monitor recording may also be utilized, although it does not include video monitoring. Prolonged recording increases the likelihood of capturing a seizure event, especially those that occur infrequently or during sleep or are provoked by situations that are difficult to replicate [65]. The patient is also instructed to provide a diary of the events of the day and to document the time of any seizures that occur [58].

Inpatient monitoring is another diagnostic option. This includes the simultaneous monitoring of EEG and video recording in an epilepsy center. Usually, the patient's AEDs are reduced or withdrawn. This setting provides the most thorough evaluation to correspond the patient's electrical activity with the clinical features of the seizures. Patients are placed in a safe setting where seizures can occur in the protected environment of experienced and accessible personnel [58]. Although the environment is well controlled with appropriately trained healthcare providers, the situation may be frightening for patients and family members.

Video/EEG recording is a critical tool in the evaluation of patients suspected of having seizures because it is the only means of reaching an incontrovertible diagnosis if clinical events occur during the recording. Video/EEG machines are relatively inexpensive today with advances in digital compression and storage technology. Cost may be reduced to a minimum by using a commercially available camcorder synchronized with the EEG [66].

In addition to the standard scalp electrodes, nasopharyngeal and sphenoidal electrodes may be inserted [38]. Sphenoidal electrodes are inserted under the zygoma and above the mandible to assist with monitoring of the temporal lobes. EEG brain mapping can also be completed during a craniotomy procedure.

In the past, EEGs were only recorded on paper. Today, these recordings can be recorded, reviewed, and stored digitally. Digital EEG recording has many advantages compared to analogue and paper EEGs, including retrospective reformatting, storage, automatic event detection, quantification, and networking capabilities. Reading of the EEG record with user-selected montages, filters, vertical scaling (gain/sensitivity), and horizontal scaling (time resolution or compression) allows for more accurate interpretation. Digital EEG also replaces the need to warehouse or microfilm paper records, enables optional additional EEG signal processing, and allows for electronic exchange of EEGs [66].

Patient education is necessary prior to the procedure. The random EEG takes approximately 30 to 40 minutes after the electrodes are attached. Total time for the procedure, including preparation, is usually between one to two hours [58]. Patients will be instructed to clean their hair prior to reporting for the scheduled test. Clean hair will allow the electrodes to hold readily. Cream rinses and conditioner should be avoided. The head is measured to allow even spacing between each of the electrodes to obtain clear and symmetrical sampling of electrical activity. It should be explained to the patient that the application of the scalp electrodes and the monitoring of brain waves are painless procedures. Typically 23 or more electrodes are attached for the basic EEG. The patients will ordinarily be required to shampoo their hair several times to remove all of the glue after the procedure [58].

If a more extensive procedure is performed, such as the insertion of sphenoidal or other electrodes, some discomfort may be experienced. In these cases, an application of topical anesthetic is often prescribed and combined with oral analgesics [65].

The EEG is not a flawless diagnostic test and does not provide a definitive diagnosis of seizures or epilepsy, although the simultaneous video/EEG monitoring procedure can provide accurate diagnostic information. However, the EEG remains an essential tool to determine if a patient is having seizures, the type of seizures, and the location of the seizures. In all situations, the patient's clinical status and history should be assessed in conjunction with any diagnosis and care plan [38; 65; 66].

Magnetic Resonance Imaging

Imaging studies are essential to determine the anatomy, function, and possible structural abnormalities in the brain. Seizures may arise from specific areas or the general regions of anatomic abnormalities. MRI is the structural imaging tool of choice [2]. MRI uses strong magnetic fields and radiofrequency electromagnetic radiation to produce images of body structures without the use of x-rays or other ionizing radiation [68]. MRI is one of the most sensitive imaging tools to assess intracranial abnormalities, including tumors, arteriovenous malformations, infections, ischemia, cysts, atrophy, cerebrovascular accidents, and hemorrhage. The hippocampus and medial temporal lobe can be visualized and evaluated with MRI [66]. Assessment of these areas is an essential component of imaging studies, as alterations in this area are often helpful to localize an epileptogenic focus. The observation of mesial temporal sclerosis often correlates with the clinical findings of temporal focal seizures. Surgically treatable lesions, such as low-grade gliomas, cortical dysplasia, and cavernous angiomas, may be detectable by MRI but not by other imaging modalities [38; 42; 68]. Intravenous contrast media may be used to increase the sensitivity and specificity of the examination.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Radiologists asserts that magnetic resonance imaging of the head without contrast is the imaging modality of choice for the assessment of new-onset seizure not related to trauma in adults 18 to 40 years of age.

(https://acsearch.acr.org/docs/69479/Narrative. Last accessed September 28, 2022.)

Strength of Recommendation: Usually Appropriate

Most patients are able to undergo an MRI scan without any difficulties. Exceptions include those patients who are markedly obese, pregnant, unable to be in a supine position for approximately one hour, or unable to tolerate a confined area. A sedative, such as diazepam, is useful in many cases to mitigate the effects of claustrophobia in patients who are too uncomfortable to enter the apparatus [69].

To ensure a safe and successful MRI, patients must remove any items or substances that contain metallic (ferromagnetic) components, including jewelry, wallets, car keys, dentures, or pins. The patient must also forgo cosmetic use, as some brands contain ferromagnetic ingredients. Patients must not have any implanted devices, such as a vagus nerve stimulator, hearing aid, cerebral aneurysm clip, or cardiac pacemaker, which might be dislodged by the procedure. This also includes susceptible metal objects, including shrapnel or other metal fragments [69]. Titanium implants are not influenced by the procedure, and orthopedic implants that have been in place for long periods of time are also usually allowable.

Computerized Axial Tomography

Computerized axial tomography (CAT), also commonly referred to as computed tomography (CT), is useful to obtain visualization of the brain at several depths. As with MRI, thin tomographic slices are visualized. Utilizing x-rays, the densities of intracranial structures can be calculated, resulting in the detection of tumors, arteriovenous malformations, hemorrhages, and other intracranial abnormalities [38]. The images produced by the CT scan, in most instances, are not as beneficial as the MRI for patients with seizures. However, the CT scan may be very useful if the patient has a new onset seizure [56]. The test can detect a wide variety of acute abnormalities and is readily available in most medical centers. The procedure is noninvasive, painless, and easier than an MRI for some patients to tolerate.

Positron Emission Tomography

Positron emission tomography (PET) presents an image of the function of the brain by quantifying the amount of glucose, oxygen, and other substances used by different regions of the brain. The resulting analysis assists in locating areas of seizure activity by noting changes in the brain's metabolism and chemistry (e.g., focused hypometabolism during interictal periods, focused hypermetabolism during ictal examinations) [66]. To conduct a PET scan, a very small amount of a short half-life radioactive material (e.g., fluorine-18-2-fluoro-2-deoxy-D-glucose, or FDG) is injected intravenously and images are immediately obtained. The patient will often be required to be supine for as long as two hours during the scan. Pregnancy may be a relative contraindication to this test, but the functional information obtained may outweigh the negative effects of the radiation [70].

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is another nuclear medicine diagnostic examination that has usefulness for patients with seizures. The SPECT scan uses a small amount of radioactive material (99mTc-HMPAO) to measure cerebral blood flow (rather than measuring cerebral metabolism, as with FDG-PET) and assist in locating areas of seizure activity. Ictal subtraction imaging is particularly helpful, especially when combined with interictal PET or MRI [2]. Comparisons of the scans may assist in determining the position and type of a seizure focus as well as help locate a possible vascular cause of the seizure [3].

Magnetoencephalography

Magnetoencephalography (MEG) is a promising, developing technology of functional brain mapping. It is noninvasive and nonhazardous and is used to identify normal and abnormal brain function in action. MEG magnetic fields are not altered by the skull and other surrounding brain structures, which permits greater accuracy and more usable and reliable localization of brain function. MEG is usually performed with simultaneous EEG recording [66]. This form of imaging is best conducted by experienced professionals at specialized epilepsy referral centers [2].

CLINICAL LABORATORY STUDIES

During an initial evaluation of a patient, a comprehensive laboratory profile should be completed. The laboratory results can assist in determining an etiology for the patient's seizures and aid in treatment decisions. If a causative factor is discovered, treatment will be essential to correct the underlying disorder. Otherwise, the laboratory results are useful in ascertaining which AED will be the most opportune for the patient. Initial laboratory evaluations should include electrolytes, a comprehensive metabolic panel, complete blood count (CBC), erythrocyte sedimentation rate, blood urea nitrogen, creatinine, and liver function tests [66]. If the history is suggestive, then toxic screens for drugs, alcohol, and toxin levels, such as lead, may be useful. A lumbar puncture may be performed to help rule out an infectious etiology of a seizure. In addition, measuring the pressure of cerebral spinal fluid is useful in the diagnosis of a possible mass lesion. Laboratory analysis of the cerebral spinal fluid may also be of benefit [71; 72].

Patients who are prescribed AEDs will often require additional laboratory testing. Depending on the medication, intermittent testing of liver function, CBC, and electrolytes may be required. Monitoring plasma blood levels of AEDs can be a useful tool to assist with the management of medication types and doses. Levels can be used to determine medication compliance, therapeutic failure, and adverse reactions. AED blood sampling should be completed at the same time for each patient, usually prior to the first dose of the day. When medication dosages are altered, the new dosage should be maintained until a steady state is achieved prior to obtaining levels [73]. Generally, four to six half-lives of the medication should be completed; for phenytoin, this time period is approximately 5 to 10 days [74]. Blood level evaluations are helpful in patient care but must always be correlated with the patient's clinical status. Patients may require a level of medication higher or lower than the stated "normal" levels. A therapeutic dose is one that controls the seizures with a minimum number of side effects, regardless of the numerical value of laboratory test results.

EPILEPSY IN SPECIFIC POPULATIONS

EPILEPSY IN CHILDREN

Seizures can begin at any age, but commonly arise before 20 years of age. Each year 25,000 to 40,000 children in the United States experience their first unprovoked seizure [75]. Children who experience seizures face unique challenges. Some children's seizures may be self-limiting and some experience no disease state, while other children develop devastating forms of epilepsy. These children's needs may vary considerably but often are related to developmental delays, depression, absence from school, and problems with their peers [76].

Children diagnosed with epilepsy will require regular office visits and evaluations. The administration of AEDs poses unique situations in children. Children grow rapidly and their weight changes, which requires alterations in medication doses. Children also have an increased metabolism and may require higher relative medication doses than those used in adults. A school-aged child may be able to assist in taking medications on their own with parental or school nurse supervision and aids such as a pillbox. AEDs may affect a child's academic performance and achievements. Interfering factors include side effects of medications, unrecognized seizures, alterations in brain function, and missed school days. Medications

such as phenobarbital may make a child sleepy and may impair learning. Adjusting medication doses or timing of the medication may assist in the child's attentiveness and ability to concentrate [75].

Febrile Seizures

Febrile seizures are the most common seizure type in children, generally occurring between 6 months and 5 years of age. Febrile seizures are tonic-clonic seizures associated with a core temperature greater than 38 degrees Celsius with no other recognizable etiology [34; 77]. Febrile seizures are classified as simple or complex [78]. Simple febrile seizures are generalized, short (last <15 minutes), do not recur within 24 hours, and have no associated focal neurologic findings [78]. In an infant younger than 6 months of age, a lumbar puncture is indicated to rule out meningitis, as typical signs may be absent [77]. Imaging and laboratory evaluations are completed if trauma or electrolyte disturbances are likely. Parents can minimize febrile convulsions with antipyretics and tepid sponge baths during febrile illnesses [78]. Usually, these children require no further intervention.

Complex febrile seizures are longer than 15 minutes in duration, occur more than once every 24 hours, indicate a more serious disease process (e.g., meningitis, encephalitis), and/or coincide with focal neurologic findings [78]. The incidence of developing nonfebrile seizures later in life increases for patients who experience complex febrile seizures in childhood [78]. There is evidence that prolonged febrile seizures may cause medial temporal sclerosis; however, contradictory results have come from several prospective and retrospective studies [79; 80; 81]. The association between febrile seizures and temporal lobe epilepsy probably results from complex interactions between several genetic and environmental factors [81].

AEDs may be instituted for children experiencing complex febrile seizures; however, prolonged daily oral anticonvulsant treatment (e.g., phenobarbital, valproate) to prevent these seizures is usually not recommended due to the potential for side effects and uncertain effectiveness [77]. The majority of children with febrile seizures do not require pharmacotherapy, and the best option may be to administer medication only while the child has a febrile illness. Diazepam (oral or rectal) may be prescribed to children especially prone to febrile seizures whenever they have a fever. This medication may lower the risk of having another febrile seizure. Although it can occasionally cause drowsiness, decreased coordination, or hyperactivity, it is usually well tolerated. Susceptibility to such side effects varies considerably [77].

West Syndrome

West syndrome is a severe epileptic disorder, usually beginning between 4 to 8 months of age [82]. The patient displays characteristic epileptic spasms, which are sudden jerky movements that often cluster. Although each child may experience spasms in a different manner, the event usually begins suddenly and occurs for a few seconds, usually upon awakening or after feeding, and attacks often occur in clusters of up to 100 spasms at a time. A typical spasm results in the patient extending his or her arms outward, with the head falling forward and the eyes gazing upward. These children have a distinctive EEG pattern called hypsarrhythmia. The EEG reveals bursts of electrical activity, including high voltage activity, with chaotic recordings [82].

There are several etiologies for West syndrome. Some causes occur before birth during the early stages of pregnancy and result in abnormal brain development. Other causes occur shortly after birth and include neonatal encephalopathy. Children may develop this syndrome due to CNS infections early in life. Some children develop epileptic spasms along with other neurologic conditions, such as tuberous sclerosis. For other children, the etiology is unclear [82].

Although some children experience developmental milestones consistent with their peers, the patient with West syndrome often suffers from intellectual disabilities and developmental delays. In the majority of children with West syndrome, the disease is very difficult to manage. Treatment with corticosteroids such as prednisone is standard, although

serious side effects may occur. Several newer AEDs, such as topiramate, may ease some symptoms. Some children have spasms as the result of brain lesions, and surgical removal of these lesions may result in improvement [82].

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is another severe epileptic disorder in children. Seizures usually begin before 4 years of age [83]. Seizure types, which vary among patients, include tonic, atonic, atypical absence, and myoclonic. There may be periods of frequent seizures mixed with brief, relatively seizure-free periods. Ordinarily, one of the seizure types causes the patient to fall. The EEG reveals characteristic slow spike-and-wave discharges. Most patients suffer from intellectual disabilities, especially if the onset occurs before 3 years of age. Many children will have a history of epileptic spasms and multiple disabilities, including cerebral palsy, blindness, and hearing impairment. In 30% to 35% of children, no cause can be found [83]. Treatment usually includes AEDs such as carbamazepine, topiramate, valproate, felbamate (adjunctive), or lamotrigine (adjunctive) [38; 83]. In 2018, a drug comprised of purified cannabidiol (Epidiolex) was approved for the treatment of Lennox-Gastaut syndrome in patients 2 years of age and older [84]. Clobazam is indicated as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome [74; 85]. There is usually no single AED that will control Lennox-Gastaut seizures. Children who improve initially may later show tolerance to a drug or have uncontrollable seizures [83].

Juvenile Myoclonic Epilepsy (JME)

JME is an autosomal inheritance disorder, meaning these children often have a family history of epilepsy. Approximately 50% to 60% of families with JME report seizures in either a direct relative or a cousin [86]. JME is one of the most common benign epileptic syndromes. The onset of this disorder occurs in childhood or early adulthood. The patient experiences myoclonic jerking of the upper extremities shortly after awakening. The patient with JME will also experience generalized tonic-clonic or absence seizures. The seizures may be aggravated by stress or sleep deprivation [87]. The selection of an AED for treatment of JME depends on several factors, including the patient's comorbidities, preferences, prior history of adverse events, and gender. Traditionally, divalproex sodium (valproic acid) has been used as first-line therapy for JME, despite not having an approved FDA indication for this condition [74]. Several studies using lamotrigine, topiramate, levetiracetam, and zonisamide (adjunctive) have shown similar efficacy, and in some cases better tolerability, than divalproex sodium [85; 86; 87]. In 2006, levetiracetam became the first drug that received FDA approval for adjunctive use specifically in JME [85; 88]. Perampanel is indicated as adjunctive treatment for patients 12 years of age or older with generalized tonic-clonic seizures [74; 85]. In studies, it is associated with reduction in myoclonic seizure frequency and no systematic cognitive deteriorations [89; 90].

EPILEPSY IN THE ELDERLY

Epilepsy affects approximately 300,000 elderly patients in the United States, which is the most rapidly growing population group with epilepsy [91]. Elderly patients with epilepsy may be difficult to manage. One of the primary concerns is that elderly patients are often prescribed multiple concomitant medications, which can predispose the patient to drug interactions and adverse effects. Another concern is that elderly individuals metabolize medications less effectively and often have an increased sensitivity to side effects. These side effects include fatigue, unsteadiness, and forgetfulness, which can lead to falls, broken bones, and a loss of independence [91]. Care should be taken to evaluate the patient and to provide therapies consistent with the patient's abilities and situation.

EPILEPSY IN WOMEN

Women may experience epilepsy differently from men due to hormonal changes and the reproductive cycle. There is an unclear relationship between female hormones and neurologic functioning. Estrogen can stimulate and progesterone can inhibit some neurons that are involved in seizure activity [92]. Women have unique needs in regard to factors related to ovulation, reproduction, and menopause that can affect epilepsy [92]. Some women experi-

ence changes in seizure activity that coincide with hormonal fluctuations. During puberty, epileptic females may experience a decrease in seizure activity, while others may initially develop an epilepsy disorder at this time. Other women report a change in seizure patterns during ovulation or around the time of menstruation. Often, patients will report an increase in number or severity of seizures during the premenstrual days and the first few days of the menstrual cycle. This phenomenon is called catamenial epilepsy [92].

Temporal lobe epilepsy is associated with an increased likelihood of disorders, such as polycystic ovarian disease, amenorrhea, early menopause, and irregular menses [92]. The hypothalamus and pituitary gland control the regulation of gonadotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone, and prolactin. Thyroid and adrenal corticoid hormones also affect ovulation and reproduction. The hormonal regulatory centers for these hormones are connected to the temporal lobe and, as a result, seizure disorders in this region may affect the regulation of these hormones. There is also evidence that some AEDs may disturb hormonal regulation, but their effects on fertility are not entirely clear [92]. Long-term use of some AEDs negatively affects bone health in women [92].

Preconception counseling is essential for all women with epilepsy who are of childbearing age. If the woman does not want children at the time of consultation, then contraceptive methods should be discussed that are acceptable to the individual. Some AEDs interfere with the metabolism of oral contraceptives, levonorgestrel implants, and medroxyprogesterone injections. When a liver enzyme-inducing medication, such as oxcarbazepine, phenytoin, carbamazepine, phenobarbital, primidone, or topiramate, is administered concomitantly with an oral contraceptive, the contraceptive will be metabolized more quickly and become less reliable [92]. Lamotrigine, levetiracetam, tiagabine, and gabapentin have no effect on the liver enzyme system and do not interfere with the effectiveness of hormonal contraception [92]. Whenever possible for women with epilepsy who are using hormonal contraception, an AED that does not enhance the liver enzyme system should be prescribed. These include valproate, felbamate, gabapentin, lamotrigine, levetiracetam, and tiagabine. If optimal seizure control requires use of an enzyme-inducing AED (i.e., carbamazepine, oxcarbazepine, phenytoin, barbiturates, or topiramate), a contraceptive agent should be prescribed that contains hormone dosages adequate to suppress ovulation. In addition, healthcare providers should recommend a barrier method of contraception [92]. Women should be educated about the reliability of each method, alternative methods, and when to notify a healthcare professional. Notification is essential when the patient experiences breakthrough bleeding, menstrual irregularities, changes in seizures, or other adverse effects.

Overall, there is a 2% to 3% risk of a woman having a child with an alteration at birth. The risk increases to 4% to 6% in women with epilepsy [93; 94]. This increased risk is due to a number of factors, including genetics, seizures during pregnancy, and the use of AEDs. As with many medications, AEDs have the most devastating fetal effects during the first few weeks of pregnancy. Unfortunately, women are not always aware of the pregnancy during this time period. The risks of AEDs are starting to be understood, but the risk of having seizures during pregnancy is less clear. There is some evidence that seizures may cause abnormal uterine contractions that could account for the increase in miscarriage, stillbirth, and hemorrhage seen in women with epilepsy [95]. These issues must be discussed with women and their partners prior to conception.

When a woman expresses her desire to have children, certain considerations are made regarding medication choices and regimens. There must be an appropriate and individualized balance between the risk of medications and the risk of seizures. In the majority of cases, the risk of seizures outweighs the risks associated with the medications. All women should be counseled to notify their healthcare providers when they become pregnant. Women must be told to continue their medications as prescribed and not to stop or alter the medications on their own [96]. The Epilepsy Foundation has recommended

that women take the following actions to increase their chances of successful pregnancy and long-term health [97]:

- Work with their healthcare provider(s) to determine the best choice of medication before they become pregnant
- Review anticonvulsant risks and benefits with their healthcare providers
- Discuss medication changes before pregnancy begins
- Take folic acid and vitamin supplementation before and during pregnancy
- Have their medication levels monitored during pregnancy
- Avoid stopping an anticonvulsant abruptly
- Explore ways of preventing other negative effects on their quality of life
- Keep current on emerging research

Women who take anticonvulsants and become pregnant are also encouraged to enroll in the AED Pregnancy Registry [98].

The addition of folic acid to the diet, especially in those women who lack adequate nutrition or are taking AEDs, may decrease the risk of abnormalities in the newborn. The patient should be provided with the reassurance that more than 90% of epileptic women who become pregnant give birth to healthy infants with no abnormalities (e.g., cleft lip, cleft palate, heart abnormalities, or spina bifida) [94]. This percentage is even higher if the pregnancy is planned in advance with the consultation of a neurologist; preconception adjustments, as needed, are made to AEDs; supplemental folic acid taken; and the woman receives early and ongoing prenatal care [92; 94].

The risk of major congenital malformations in the offspring of women with epilepsy is possibly decreased by folic acid supplementation. The American Academy of Neurology and the American Epilepsy Society recommend that preconception folic acid supplementation in women with epilepsy be considered to reduce the risk of major congenital malformations.

(https://www.aan.com/Guidelines/home/GuidelineDetail/333. Last accessed September 28, 2022.)

Strength of Recommendation: C (Possibly effective for the given condition in the specified population)

Data from multiple studies have demonstrated an increased risk to the unborn child with the use of valproate and suggested that it is not the best first choice for women of childbearing age. Overall, valproate and carbamazepine appear to pose the greatest risk of neurologic abnormalities [74]. However, when no other anticonvulsants work to control an individual's seizures, then the risk may be reduced by limiting the dose during pregnancy. The AAN and the American Epilepsy Society (AES) have recommended that women with epilepsy avoid taking valproate during pregnancy and that they also avoid taking more than one epilepsy drug at a time (i.e., polytherapy) during pregnancy if possible. Valproate use, and to a lesser extent polytherapy, have been linked to an increased risk for birth defects and an increased risk for developmental delay in children after exposure during pregnancy [74; 92; 99]. The FDA has issued a reminder to healthcare professionals about these risks, especially with exposure during the first 12 weeks of pregnancy [100]. Nevertheless, women taking any AED should not discontinue the drug on their own and should consult with their physician if they are, or may become, pregnant [92; 99].

The pregnant epileptic woman will require early prenatal care and possible genetic counseling. Some neonates develop coagulation disorders that are related to vitamin K deficiency. These disorders are usually noted in mothers taking phenytoin, phenobarbital, and primidone throughout the preg-

nancy. Newborns exposed to AEDs routinely receive vitamin K at delivery, as do all newborns. However, the AAN has concluded that there is inadequate evidence to determine whether prenatal vitamin K supplementation in women with epilepsy reduces the risk of neonatal coagulation disorders [101].

Although AEDs may be found in breast milk, their presence does not preclude breastfeeding for most women. Primidone and levetiracetam transfer into breast milk in amounts that may be clinically important, but valproate, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts [74; 101]. Caution with phenobarbital use has been recommended [74]. In some cases, infants of breastfeeding women experience somnolence or irritability, especially with phenobarbital. Supplemental bottle feedings may be recommended.

During menopause, seizure characteristics may change in women. Many women report an improvement in their condition, others state that the seizures worsen, and some report no change [92]. Hormonal replacement therapy must be carefully considered and balanced with other risk factors, such as cardiac disease, osteoporosis, uterine cancer, breast cancer, and the patient's epilepsy [92]. In general, patients receiving supplemental estrogen should also receive progesterone to assist with seizure control. More research is required to understand the complex issues related to women and epilepsy. Research should focus on these unique issues in regard to management, medications, and treatment [102].

EPILEPSY IN MEN

Men with epilepsy may also experience cyclic or hormonal fluctuations in their seizure patterns. Fertility and reproductive changes affected by epilepsy in men are not well understood and appear to be multifactorial and common. Psychosocial complications associated with epilepsy may also affect reproductive health and sexuality [103]. Approximately one-third of men with epilepsy report having trouble obtaining and maintaining an erection [11]. Clinicians should investigate such problems, not only because of their multifactorial nature, but also because both patients and physicians often fail to recognize or may be reluctant to acknowledge them. This may be particularly true in men whose epilepsy had its onset before puberty, because they may lack subjective awareness about normal sexual response and function [103].

There is hope that the medications for erectile dysfunction may help with this problem; however, at this time there is insufficient evidence to make an estimate of any benefit. Medications (or surgery, in some cases) for erectile dysfunction surgery may be useful; some researchers have cautioned against concentrating only on hormone levels to explain sexual dysfunction and have encouraged that future studies include measures of quality of life, anxiety, and depression among men with epilepsy [103; 104].

THERAPEUTIC MODALITIES

Although prevention of epilepsy is the ultimate goal, this is not always possible. However, there is a variety of treatment options. Comprehensive treatment is an important aspect of care for all patients with epilepsy. Managing the disorder improves the quality of life, and the consequences of not treating may be great. Seizures that go untreated or are poorly controlled have an increased risk of becoming more severe or more difficult to manage. Treatment recommendations tend toward more aggressive management and earlier surgical evaluation for patients with epilepsy.

PHARMACOLOGIC MANAGEMENT

The utilization of AEDs is the mainstay of therapeutic options. The effectiveness of AEDs relies on the ability to classify the seizure type by its clinical presentation, history, and diagnostic test findings. It is important to know the correct seizure type, as some AEDs will be more effective or will exacerbate certain seizures or seizure syndromes (***Table 3***). Other factors to consider include patient age, gender, long-term goals, health history, drug interactions, potential side effects, and psychologic history. The goal of AEDs is to reduce or control seizure activity with no side effects, not to cure the disorder [105].

COMMON MEDICATIONS/SEIZURE TYPES						
Medication	**Focal Onset**	**Tonic-Clonic**	**Absence**	**Myoclonic**	**Atonic**	**Other**
Brivaracetam	X					
Carbamazepine	X	X				
Cenobamate	X	X	X	X	X	Lennox-Gastaut (adjunctive)
Clobazam	X		X	X		Lennox-Gastaut
Clonazepam	X		X	X		Lennox-Gastaut
Diazepam	X	X	X	X	X	Status epilepticus (adjunctive)
Divalproex sodium	X		X			
Eslicarbazepine	X					
Ethosuximide			X			Juvenile myoclonic
Felbamate	X	X			X	Lennox-Gastaut
Fenfluramine						Dravet syndrome Lennox-Gastaut
Gabapentin	X					
Lacosamide	X					Lennox-Gastaut Status epilepticus[a]
Lamotrigine	X	X				Lennox-Gastaut Juvenile myoclonic
Levetiracetam	X	X		X		Status epilepticus[a] Juvenile myoclonic
Lorazepam	X[a]	X		X	X	Status epilepticus Juvenile myoclonic
Midazolam						Status epilepticus[a]
Oxcarbazepine	X	X				
Perampanel	X	X				
Phenobarbital	X	X				Lennox-Gastaut Status epilepticus
Phenytoin	X	X				Status epilepticus
Pregabalin	X					
Primidone		X		X		Juvenile myoclonic
Rufinamide						Lennox-Gastaut (adjunctive)
Stiripentol						Dravet syndrome (in combination with clobazam)
Tiagabine	X					
Topiramate	X	X				Lennox-Gastaut
Valproic acid	X	X	X	X	X	Lennox-Gastaut Juvenile myoclonic

Table 3 continues on next page.

COMMON MEDICATIONS/SEIZURE TYPES *(Continued)*						
Medication	**Focal Onset**	**Tonic-Clonic**	**Absence**	**Myoclonic**	**Atonic**	**Other**
Vigabatrin	X (refractory)					Epileptic spasms
Zonisamide	X					
Cannabidiol						Lennox-Gastaut Dravet syndrome
[a]Use is investigational. As medication indications and dosages vary, please consult the latest literature for changes to the recommendations.						
Source: [74; 106]						*Table 3*

In general, focal seizures are more difficult to treat with medications than generalized seizures. AEDs allow approximately 70% of epileptic patients to achieve seizure control with minimum side effects. Another 20% to 30% can achieve good control with current medications, although some adverse effects may be experienced [106]. A patient's response to the first AED has been found to be an indicator of the success of any AED [107; 108]. If a patient does not respond well with the first medication due to lack of efficacy, then it is likely that the patient may have refractory epilepsy [106]. However, if treatment failure is due to side effects or an idiosyncratic reaction, then alternative AEDs or other treatment options (e.g., surgery) may be more successful [106; 107].

AEDs assist patients by stabilizing nerve cell membranes and preventing the spread of abnormal electrical discharges. Many of the medications require a therapeutic level of effectiveness to provide the best seizure control with minimum side effects. Treatment with medications usually focuses on using an adequate dose of a single medication (i.e., monotherapy) rather than smaller doses of several drugs. Monotherapy is the goal for most patients due to the benefits of improved drug compliance, reduced cost of medication and laboratory evaluations, lower risk of adverse effects, and lessened chance of drug interactions. Monotherapy successfully manages nearly 50% of epilepsy patients and is particularly desirable for certain special patient populations, such as women, the elderly, and patients with comorbid conditions [106; 109; 110; 111]. Polytherapy offers no advantage over monotherapy for the majority of patients with epilepsy and may substantially increase the risk of AED toxicity and seizure aggravation. Polytherapy may be necessary, however, for patients who develop refractory epilepsy [34; 110; 111; 112].

If the first AED that is attempted proves undesirable due to lack of efficacy (i.e., the patient fails to become seizure-free) or adverse effects, the first medication may be tapered off, while a second is slowly added [110; 111; 113]. When switching from one AED to another, choosing one with a different mechanism of action may increase the likelihood of a successful treatment response [111]. After several single medications have been used that are consistent with the patient's seizure type, polytherapy may be attempted. It is common for a refractory patient to require a daily regimen of two or three AEDs. Adequate treatment may take several weeks or months to become beneficial [110; 111]. During treatment, healthcare providers should consider the possibility of patient noncompliance, incorrect diagnosis, and other factors that may contribute to the ineffectiveness of a medication choice [110].

Side effects are common with many AEDs (***Table 4***). These adverse effects include, but are not limited to, drowsiness, nausea, visual changes, and fatigue. Some adverse effects are related to the dose of the medications, while other effects, such as allergic-type reactions, occur regardless of the dose. With some medications, certain side effects are noted when a drug is first initiated or with a change in dosage. Depending on the type of side effect, it may abate with time. For example, dizziness, a common side effect with carbamazepine, often improves with continuation of the medication.

AED ADVERSE EFFECTS		
AED	**Possible Side Effects**	**Possible Idiosyncratic Effects**
Brivaracetam	Dizziness, drowsiness, psychiatric disturbance, sedated state	Angioedema, bronchospasm
Cannabidiol	Skin rash, weight loss, decreased appetite, drowsiness, fatigue	Suicidal ideation
Carbamazepine	Dizziness, visual changes, headache, lethargy, anorexia, nausea, ataxia, syncope	Hepatitis, hyponatremia, skin photosensitivity, systemic lupus erythematosus
Cenobamate	Somnolence, dizziness, fatigue, diplopia, headache	Eosinophilia, rash, lymphadenopathy
Clobazam	Drowsiness, lethargy, aggressive behavior, irritability, upper respiratory tract infection	Abdominal distention, anemia, eosinophilia, leukopenia
Clonazepam	Drowsiness, ataxia, behavioral changes, movement disorders, speech alterations, hypersecretion in bronchioles, amnesia, weight gain	Hirsutism, anorexia, anemia, tremor, blurred vision
Diazepam	Somnolence	Paradoxical excitement
Divalproex sodium	Alopecia, abdominal pain, infection, dizziness, visual disturbance	Bradycardia, skin photosensitivity, aplastic anemia, hepatic failure
Eslicarbazepine	Dizziness, drowsiness, headache, nausea, diplopia	Agranulocytosis, angioedema, leukopenia
Ethosuximide	Gastrointestinal (GI) distress, drowsiness, sedation, headache, anorexia	Liver disorders, systemic lupus erythematosus, psychosis, depression, leukopenia, Stevens-Johnson syndrome
Felbamate	Anorexia, vomiting, insomnia, weight loss, fever, ataxia, headache	Aplastic anemia, liver failure, Stevens-Johnson syndrome
Fenfluramine	Aortic insufficiency, increased blood pressure, weight loss, asthenia, fever	Heart valve disease, pulmonary hypertension
Gabapentin	Somnolence, dizziness, ataxia, nystagmus, weight gain, rash, nausea, vision changes, tremor, slurred speech, peripheral edema	Acute renal failure, cardiac anomalies
Lacosamide	Dizziness, diplopia, headache, ataxia, vomiting, nausea, vertigo, blurred vision	Multiorgan hypersensitivity reactions, syncope
Lamotrigine	Fatigue, drowsiness, ataxia, dizziness, headache, GI distress, visual changes, alopecia, pruritus	Disseminated intravascular coagulation, Stevens-Johnson syndrome, fetal abnormalities, toxic epidermal necrolysis
Levetiracetam	Somnolence, difficulty with coordination, dizziness	Psychosis
Lorazepam	Respiratory depression, hypotension, central nervous system depression	Asthenia, increased salivation, vertigo
Midazolam[a]	Severe respiratory depression, apnea	Amnesia, confusion, excessive salivation, hyperventilation, rash
Oxcarbazepine	Dizziness, nausea, headache, somnolence, upper respiratory tract infections, constipation, dyspepsia, ataxia, nervousness	Rash
Perampanel	Peripheral edema, dizziness, vertigo, vomiting/nausea	Acute psychosis, delirium, hallucination
Phenobarbital	Sedation, mental dullness, cognitive impairment, ataxia	Hyperactivity, rash
Phenytoin	Dizziness, drowsiness, nystagmus, ataxia, hypotension, electrocardiogram changes	Gingival hyperplasia, hirsutism, coarsening of facial features, acne, rash, peripheral neuropathy
Pregabalin	Dizziness, somnolence, visual disturbances, peripheral edema	Anemia, heart failure, Stevens-Johnson syndrome
Primidone	Sedation, mental dullness, cognitive impairment, ataxia, cardiovascular	Hyperactivity, rash

Table 4 continues on next page.

AED ADVERSE EFFECTS *(Continued)*		
Rufinamide	Shortened QT interval, nausea/vomiting, dizziness, drowsiness, fatigue	Stevens-Johnson syndrome, agranulocytosis
Stiripentol	Drowsiness, agitation, ataxia, weight loss, tremor	Suicidal ideation, CNS depression
Tiagabine	Difficulty with concentration, dizziness, nervousness, somnolence, nausea, tremor	New-onset seizures and status epilepticus with unlabeled use, generalized weakness, rash
Topiramate	Somnolence, dizziness, ataxia, speech disorders, confusion, visual changes, memory problems, difficulty with concentration and attention	Mood changes, renal calculi
Valproate	GI distress, lethargy, fine tremor, hematologic problems	Weight gain, alopecia, hepatotoxicity, cardiac abnormalities, pancreatitis
Vigabatrin	Somnolence, headache, fatigue, upper respiratory tract infection	Psychosis, deafness, facial edema, respiratory failure
Zonisamide	Drowsiness, anorexia, alterations in coordination/thinking	Alopecia, cardiac abnormalities, facial edema, immunodeficiency
[a]Use of midazolam is investigational. As medication indications and dosages vary, please consult the latest literature for changes to the recommendations.		
Source: [74]		*Table 4*

Patient education is crucial to obtain medication adherence and provide optimum patient care. The patient should receive instruction on the type, dose, and potential side effects of each medication [111]. The patient should also understand that the medication is to be taken every day, on time, and as prescribed. Although brand and generic drugs are comprised of the same active compounds, their absorption may vary and patients should be cautioned not to interchange the medications. To avoid undesirable drug interactions, all professionals writing prescriptions, including dentists, should be aware of all medications a patient is taking. The patient should be informed that many medications interact with other CNS depressants, including alcohol. Patients should be requested to bring medication bottles with them at each visit.

According to the American Academy of Neurology and the American Epilepsy Society, patients should be advised that their risk for antiepileptic drug adverse events ranges from 7% to 31% and that these adverse events are predominantly mild and reversible.

(https://www.aan.com/Guidelines/home/GetGuidelineContent/688. Last accessed September 28, 2022.)

Strength of Recommendation/Level of Evidence: B (Probably useful based on at least randomized controlled study or two consistent cohort studies.)

As mentioned, monitoring of drug levels is an important aspect of anticonvulsant therapy [111]. Patients should be informed of the frequency and necessity of blood draws. Many AEDs have a common range of levels associated with the desired therapeutic effects with the least likelihood of adverse reactions. Occasionally, patients may benefit from a level outside the ranges and have intolerable side effects at low levels (***Table 5***). An overview of several specific medication dosages and indications is available in ***Table 6***.

AED RANGES AND HALF-LIVES		
AED	**Reference Range[a]**	**Half-Life (Hours)**
Brivaracetam	0.5–0.9 mg/L	9
Cannabidiol	Not established	56–61
Carbamazepine	4–12 mcg/mL	Variable (single dose 25–65; chronic dose 12–17)
Cenobamate	Not established	50–60
Clobazam	0.03–0.3 mg/L	36–42
Clonazepam	15–70 ng/mL	17–60
Diazepam	0.2–1.5 mcg/mL	20–50
Divalproex sodium	50–100 mcg/mL	9–19
Eslicarbazepine	Not established	13–20
Ethosuximide	40–100 mcg/mL	50–60
Felbamate	Not established (30–60 ng/mL recommended)	20–23 (varies by dose)
Fenfluramine	Not established	20
Gabapentin	Not established (2–10 ng/mL recommended for seizure control)	5–7
Lacosamide	200–400 mg	13
Lamotrigine	Not established (1–13 mcg/mL common seizure control range)	25–33
Levetiracetam	12–46 ng/mL	6–8
Lorazepam	50–240 ng/mL	12.9
Midazolam	Varies	1.8–6.4
Oxcarbazepine	3–35 ng/mL	1–2.5
Perampanel	Not established	105
Phenobarbital	10–40 ng/mL	53–118
Phenytoin	10–20 ng/mL	22 (oral dose)
Pregabalin	Not established	6.3
Primidone	5–12 ng/mL	5–16
Rufinamide	3–30 mg/L	6–10
Stiripentol	4–22 mg/L	4.5–13
Tiagabine	Not established; varies with dosage, concomitant drugs, laboratory	2–5 when administered with enzyme inducers; 7–9 without
Topiramate	Not established (2–25 ng/mL expected)	21
Valproate	50–100 ng/mL	9–19
Vigabatrin	Not established	10.5
Zonisamide	Not established (10–40 ng/mL suggested)	63
[a]All ranges presented in this table are for adults. As medication indications and dosages vary, please consult the latest literature for changes to the recommendations.		
Source: [74]		*Table 5*

AED ADMINISTRATION (ADULTS)			
Medication	**Indications**	**Usual Dose[a]**	**Dosage Forms**
Brivaracetam	Focal	Initial: 50 mg twice/day May increase to 25 mg twice/day Maximum: 200 mg/day	Solution Tablet
Cannabidiol	Lennox-Gastaut Dravet syndrome	Initial: 2.5 mg/kg twice/day Increase after 1 week to 5 mg/kg twice/day Maximum: 10 mg/kg twice/day	Solution
Carbamazepine	Generalized (tonic-clonic) Focal Mixed seizure patterns	Initial: 400 mg in two divided doses (tablets) or four divided doses (oral suspension) Increase by 200 mg weekly until optimum response Usual dose: 800–1,200 mg/day Maximum: 1,600 mg/day	Tablet Chewtab Extended-release tablet Suspension Extended-release capsule
Cenobamate	Focal	Initial: 12.5 mg/day for two weeks, then double every two weeks until maintenance dose is achieved. Maintenance: 200 mg/day Maximum: 400 mg/day	Tablet
Clobazam	Lennon-Gastaut	Initial: 5 mg twice/day for one week or more Increase based on response to 10 mg twice/day for one week or more Then increase to 20 mg twice/day thereafter	Film Suspension Tablet
Clonazepam	Generalized (myoclonic, absence, atonic) Lennox-Gastaut Akinetic	Initial: 1.5 mg in three divided doses Usual dose: 2–8 mg/day Maximum: 20 mg/day in divided doses	Tablet Orally disintegrating tablet
Diazepam	Generalized (myoclonic, absence, atonic) Status epilepticus	Initial: 2–10 mg once May be repeated as needed	Syrup Oral solution Tablet Rectal gel
Divalproex sodium	Focal Generalized	Initial: 10–15 mg/kg/day for focal seizures 15 mg/kg/day for absence seizures in 1 to 4 divided doses Increase by 5–10 mg/kg/day at weekly intervals Maximum: 60 mg/kg/day	Capsule Tablet
Eslicarbazepine	Focal	Initial: 400 mg once/day. Increase in weekly increments of 400–600 mg based on response Maintenance: 800–1,600 mg/once day	Tablet
Ethosuximide	Generalized (absence)	Initial: 500 mg/day Increase 250 mg as needed every four to seven days Maximum: 1.5 g/day	Capsule Oral solution
Felbamate	Focal Lennox-Gastaut	Initial: 1,200 mg/day in three or four divided doses Increase 600 mg every two weeks Usual dose: 2,400–3,600 mg/day	Suspension Tablet
Fenfluramine	Lennox-Gastaut Dravet syndrome	Initial: 0.1 mg/kg twice/day Day 7: Increase as tolerated to 0.2 mg/kg twice/day Day 14: Increase as tolerated to 0.35 mg/kg twice day Maximum: 26 mg/day	Solution

Table 6 continues on next page.

AED ADMINISTRATION (ADULTS) *(Continued)*			
Gabapentin	Focal	Initial: 300 mg 3 times/day Increase based on response/tolerability	Capsule Tablet Solution
Lacosamide	Focal	Initial: 50 mg twice daily May be increased at one-week intervals 100 mg/day Maintenance: 200–400 mg/day Maximum: 400 mg/day	IV solution Tablet Oral solution
Lamotrigine	Focal Lennox-Gastaut	Initial: 25 mg/day for two weeks; then increase to 50 mg/day for two weeks as adjunct Maintenance: 225–375 mg/day in two divided doses	Tablet Chewtab Dispersible tablet Extended-release tablet
Levetiracetam	Generalized (tonic-clonic, myoclonic) Focal	Initial: 500 mg two times/day Increase 500 mg every two weeks to recommended 1,500 mg twice daily dose Maximum: 3,000 mg/day	IV solution Oral solution Tablet Disintegrating soluble tablet Extended-release tablet
Lorazepam	Status epilepticus	4 mg/dose slow IV (maximum rate: 2 mg/minute) Maximum: 8 mg/dose May repeat in 10 to 15 minutes	Injection solution Oral concentrate Tablet
Midazolam	Status epilepticus (investigational)	Initial: 0.2 mg/kg followed by continuous infusion of 0.05–2 mg/kg/hour titrated to cessation of seizures. If breakthrough status epilepticus, administer bolus of 0.1–0.2 mg/kg and increase infusion rate by 0.05–0.1 mg/kg/hour every three to four hours	Injection solution
Oxcarbazepine	Focal	Initial: 600 mg in two divided doses Maintenance dose: 1,200 mg/day in two divided doses Maximum: 1,200 mg/day	Suspension Tablet Extended-release tablet
Perampanel	Generalized (tonic-clonic) Focal	Initial: 2 mg once/day at bedtime Increase daily dose by 2 mg once/day at weekly intervals Maintenance dose: 8–12 mg once/day at bedtime	Suspension Tablet
Phenobarbital	Generalized (tonic-clonic) Focal Status epilepticus	Initial: 15–20 mg/kg slow IV Maximum: 30 mg/kg Maintenance: 50–100 mg two to three times/day (oral) or 1–3 mg/kg/day in divided doses (IV)	Tablet Elixir Injection solution Oral solution
Phenytoin	Generalized (tonic-clonic) Focal Status epilepticus	Initial: 10–15 mg/kg, not exceeding 50 mg/minute (IV), or 100 mg three times/day (oral) Maintenance: 100 mg (oral or IV) every six to eight hours Usual dose: 300–600 mg/day	Capsule Chewtab Suspension Injection solution
Pregabalin	Focal	Initial: 150 mg/day in divided doses May increase until optimum response Maximum: 600 mg/day	Capsule Oral solution

Table 6 continues on next page.

AED ADMINISTRATION (ADULTS) *(Continued)*			
Medication	**Indications**	**Usual Dose**[a]	**Dosage Forms**
Primidone	Generalized (tonic-clonic) Focal	Initial: 125–250 mg at bedtime Maximum: 2 g/day in divided doses Usual: 750–1,500 mg/day in three or four divided doses	Tablet
Rufinamide	Lennox-Gastaut	400–800 mg/day in 2 equally divided doses Increase by 400–800 mg/day every other day to maximum dose of 3.2 g/day in 2 equally divided doses	Suspension Tablet
Stiripentol	Dravet syndrome (in combination with clobazam)	Usual: 50 mg/kg/day in 2 to 3 divided doses Maximum: 3 g/day	Capsule
Tiagabine	Focal	Initial: 4 mg once daily for one week Increase until optimum response Maintenance: 32–56 mg/day in divided doses	Tablet
Topiramate	Generalized (tonic-clonic) Focal Lennox-Gastaut	Initial: 25–50 mg/day for one week Increase slowly Maintenance: 100–200 mg twice daily Maximum: 400 mg/day	Tablet Capsule Capsule (sprinkle) Extended-release capsule (sprinkle)
Valproate	Generalized (tonic-clonic, absence, myoclonic, atonic) Focal	Initial: 10–15 mg/kg/day in divided doses Maintenance: 30–60 mg/kg/day in divided doses Maximum: 60 mg/kg/day	Capsule Delayed-release capsule Syrup Oral solution Delayed-release tablet Extended-release tablet IV solution
Vigabatrin	Focal Epileptic spasm	Initial: 500 mg twice daily Maintenance: 2–3 g/day Maximum: 3 g/day	Tablet Powder packet
Zonisamide	Focal	Initial: 100 mg/day Maintenance: 300–400 mg/day with two weeks between 100 mg/day adjustments Maximum: 400 mg/day	Capsule
[a]All doses presented in this table are for adults, and doses may vary. As medication indications and dosages vary, please consult the latest literature for changes to the recommendations.			
Source: [74]			*Table 6*

It must be remembered that treatment of seizures and epilepsy is accomplished on an individual basis with each patient. Appropriate drugs, doses, and side effects may vary with each individual [74; 114; 115].

As noted, AEDs represent the main therapeutic approach for patients with epilepsy. Other labeled indications include bipolar disorder, mania, neuralgia, migraine, and neuropathic pain. An increase in off-label use of AEDs has also been reported. This wide range of indications and common use in patients with or without psychiatric co-morbidities has raised questions about the safety of AEDs. In 2008, the FDA published a meta-analysis that included data from 199 placebo-controlled trials of 11 AEDs (carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide) used either as monotherapy or as adjuvant therapy.

The FDA found that patients receiving an AED had approximately twice the risk of suicidal behavior or ideation (0.43 per 100) compared with patients receiving placebo (0.22 per 100). As a result of the findings, the FDA required that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidal thoughts and behavior. The agency also stated that patients, their caregivers, and their families be informed of these risks and advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm [74; 116; 117].

Although the FDA found that the results for individual drugs were generally consistent with the overall result, some researchers felt that this meta-analysis was not sufficiently large to fully investigate individual AEDs. Additional exploratory analysis of the risk of suicidal acts and combined suicidal acts or violent death associated with individual AEDs has suggested that the use of gabapentin, lamotrigine, oxcarbazepine, and tiagabine, compared with the use of topiramate, may be associated with an increased risk of suicidal acts or violent deaths [116; 117].

Brivaracetam

Brivaracetam was approved by the FDA in 2016 as an add-on treatment for focal seizures in patients 16 years of age and older [74]. The precise mechanism of brivaracetam is unknown. The agent displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the antiseizure effect. It has high lipid solubility and rapid brain penetration, with engagement of the target molecule, SV2A, within minutes of administration [74]. Brivaracetam is usually started at 50 mg twice per day. Dosing can be lowered to 25 mg twice per day if side effects occur. The dose is then increased as needed to the recommended dose of 100 –200 mg daily. Dosing for individuals with mild-to-severe hepatic impairment is 25 mg twice per day and increased to 75 mg twice per day [74].

Cannabidiol

Cannabidiol (Epidiolex) is indicated for treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome [74]. In 2020, the FDA approved a new indication for cannabidiol, adding treatment of seizures associated with tuberous sclerosis complex [118]. The exact antiseizure mechanisms of action of cannabidiol is unknown; however, it does not appear to involve its effects on cannabinoid receptors [74]. Food and milk increase the absorption of the agent. It is metabolized primarily in the liver and gut by CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7 to active metabolite 7-OH-CBD and then to inactive metabolite 7-COOH-CBD. Idiosyncratic side effects include suicidal ideation and suicidal tendencies. Obtain AST, ALT, and total bilirubin at baseline and one, three, and six months after initiation and then periodically. Dosage adjustment may be needed in patients with hepatic dysfunction [74].

Carbamazepine

The mechanism of action of carbamazepine is generally recognized to be the inhibition of nerve impulses by repressing sodium ion influx across cell membranes in the motor cortex. This medication is used for first-line therapy in the treatment of generalized tonic-clonic and focal seizures. There is no indication for the use of carbamazepine in absence or myoclonic seizures [74; 119].

Carbamazepine treatment is initially started with a low dose and tapered upward to prevent the occurrence of adverse effects and to allow stabilization of drug levels. When discontinuing therapy, a down titration is recommended [119]. The primary side effects of carbamazepine are lethargy, dizziness, and GI side effects. A reduction in these side effects is often noted during the first few weeks of therapy. Other adverse effects include headache, ataxia, visual changes, mood alterations, and difficulty concentrating [74].

Idiosyncratic side effects include hepatitis, hyponatremia, skin photosensitivity, and systemic lupus erythematosus. The life-threatening side effects of carbamazepine include agranulocytosis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome (SJS). The risk of TEN and SJS is highest in patients of Asian descent who have a genetic risk factor [74; 119]. Patients will require monitoring of the CBC and for the appearance of a rash [74; 105].

Most of the absorbed carbamazepine is metabolized to carbamazepine 10, 11 epoxide (CBZ-E) by the liver. The metabolism of carbamazepine changes with the duration of treatment, and after several weeks of dosing, the half-life is often reduced [74]. Metabolism occurs more rapidly in children than in adults [34; 119]. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established [119]. Monitoring of the parent drug and epoxide levels is important to evaluate the drug's metabolism and to provide the appropriate dose. Carbamazepine is an effective inducer of drug metabolism, and there are drug interactions with a variety of medications [74; 105; 119]. These interactions may raise or lower carbamazepine levels [74; 119].

The absorption of carbamazepine can be slow and erratic, resulting in peak levels of the drug at various time intervals [74]. Tegretol XR, Equetro, and Carbatrol are long-acting forms of carbamazepine. Patients often have improved tolerance to side effects with the delayed release capsules and the improved steady state drug levels. Carbatrol is believed to have less variability in regard to the absorption of carbamazepine. Carbatrol is not effective and may have negative effects for generalized absence and myoclonic seizures.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Clinical Excellence recommends considering lamotrigine or levetiracetam as first-line monotherapy for children, young people, and adults with focal seizures.

(https://www.nice.org.uk/guidance/ng217. Last accessed September 28, 2022.)

Strength of Recommendation: Expert Opinion/ Consensus Statement

Cenobamate

In 2019, the FDA approved cenobamate for the treatment of partial-onset seizures in adults [120]. Two randomized, double-blind, placebo-controlled studies involving 655 adults assessed the efficacy and safety of cenobamate. During the trials, doses of 100 mg, 200 mg, and 400 mg daily reduced the percent of seizures per 28 days compared with the placebo group [120]. The recommended maintenance dose of cenobamate, following a titration period, is 200 mg daily; however, some patients may need an additional titration to a maximum of 400 mg daily based on clinical response and tolerability [120].

As with other AEDs, cenobamate may be associated with an increased risk of suicidal thoughts or behavior. The most common side effects include somnolence, dizziness, fatigue, diplopia, and headaches [120].

Clobazam

The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of gamma-aminobutyric acid-ergic (GABAergic) neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor. Peak plasma levels of clobazam are dose-proportional over the dose range of 10 – 80 mg. Clobazam is converted to *N*-desmethylclobazam, which has about one-fifth the activity of clobazam. Clobazam is rapidly and extensively absorbed following oral administration. Clobazam is lipophilic and distributes rapidly throughout the body. Clobazam is extensively metabolized in the liver, with

approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug [74]. Common adverse reactions include constipation, somnolence or sedation, pyrexia, lethargy, and drooling. Serious dermatologic reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis [74].

Clonazepam

Clonazepam is a benzodiazepine that is useful for the treatment of Lennox-Gastaut syndrome and myoclonic, absence, and atonic seizures. Clonazepam may be used alone but is most often used in combination with other AEDs. It is also used in the treatment of absence seizures after other medications have proved ineffective. Although the exact mechanism of action is unknown, all benzodiazepines act as CNS depressants by facilitating the action of gamma-aminobutyric acid (GABA). The enhancement of the action of GABA increases the seizure threshold by reducing the ability of neurons to depolarize and suppressing the spread of seizures [74]. This medication should be started at a low dose then slowly titrated upward. Drug monitoring is not frequently completed due to large individual variations between therapeutic clinical outcomes and adverse effects. Drowsiness and ataxia are very common side effects, often resulting in intolerance to the medication. Other common adverse effects include behavioral disturbances, cognitive impairment, hypersecretion of bronchial fluid, weight gain, and excessive salivation [74; 119].

Patients eventually develop tolerance to the medication's antiepileptic effects, which often necessitates an increase in dosing. However, higher doses do not always correspond with increased seizure control. Removal of the medication should be considered cautiously, as abrupt discontinuation may lead to poor seizure control or status epilepticus [119]. Drug intolerance and difficulty with discontinuing this medication make clonazepam an unpopular first choice for most seizure types. Drug interactions are less common with clonazepam compared to the majority of AEDs.

Diazepam

Diazepam is a benzodiazepine that is beneficial during uncontrolled seizure activity and status epilepticus. This benzodiazepine is not used for the chronic treatment of epilepsy but is essential for the acute treatment of seizure events. Diazepam suppresses generalized seizure activity and limits the spread of electrical discharges. The mechanism of action is related to increasing the effects of GABA, an inhibitory neurotransmitter [74].

Diazepam is a CNS depressant, and somnolence is a common adverse effect of the medication. The potential for abuse is greater for benzodiazepines than many of the other AEDs. Idiosyncratic side effects include a paradoxical excitement. Respiratory suppression is a rare but life-threatening possibility [74].

In addition to tablet and intravenous injection formulations, rectal diazepam is available for administration as a gel. This formulation is useful for patients who experience severe seizures with the potential of status epilepticus [74; 119]. The administration of this benzodiazepine may shorten the duration of seizures and prevent recurring seizures. Ultimately, the patient may have a reduced number of emergency visits with an improved quality of life. A well-trained caregiver and close supervision are essential.

Divalproex Sodium

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA). Valproate is metabolized almost entirely by the liver. Usually, less than 15% to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine [74].

Monitor liver enzymes at baseline and frequently during therapy, especially during the first six months. Monitor for signs and symptoms of hepatotoxicity (e.g., malaise, weakness, facial edema). Evaluate pregnancy status in patients who could become pregnant [74]. Common adverse effects include fatigue, dizziness, upset stomach, tremor, hair loss, and weight gain [74].

Eslicarbazepine

Eslicarbazepine is indicated for treatment of focal seizures as monotherapy or adjunctive therapy [74]. Serious dermatologic reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported in association with this agent. Risk factors for development of serious and potentially fatal dermatologic reactions have not been identified. The precise mechanism(s) by which eslicarbazepine exerts anticonvulsant activity is unknown but is thought to involve inhibition of voltage-gated sodium channels. Eslicarbazepine is rapidly and extensively metabolized by hydrolytic first-pass metabolism to the major active metabolite eslicarbazepine and minor active metabolites (R)-licarbazepine and oxcarbazepine; active metabolites are further metabolized to inactive glucuronides. Idiosyncratic reactions include agranulocytosis, anaphylaxis, angioedema, leukopenia, and prolongation of the PR interval on ECG [74].

Ethosuximide

Ethosuximide is effective in suppressing the paroxysmal spike-and-wave pattern that occurs in absence seizures. Furthermore, it has been found to depress nerve transmission in the motor cortex and increase the seizure threshold [74]. Ethosuximide is effective for the treatment of absence seizures; however, it is not efficacious for other forms of generalized seizures or focal seizures. Due to the documented hepatotoxicity of valproate in children, ethosuximide is often the preferred first choice. The medication is begun at a low dose, then increased to a maintenance dose. Administering ethosuximide in an incremental fashion (and with food or milk) decreases GI side effects [74]. Nausea, anorexia, drowsiness, and headache are the primary adverse reactions. These symptoms often decrease with continued dosing of the medication or by reducing the dose. Unusual reactions, such as aggression, delusional paranoid disorder, depression (with overt suicidal intentions), leukopenia, and rash, have been reported with this drug [74]. No harmful effects on intellectual functioning have been reported. There are also fewer drug interactions with this medication, especially with other AEDs.

Felbamate

In 1993, felbamate was one of the first "newer" AEDs to be approved by the FDA. However, it is no longer recommended as a first-line AED [74; 115].

The mechanism of action in felbamate is unknown but has properties in common with other marketed anticonvulsants. It is believed to involve an antagonistic effect of N-methyl-D-aspartate (NMDA) receptors. The inhibition of NMDA receptors may block excitatory amino acids and suppress seizure activity [74]. These actions result in an increase in seizure threshold and a reduction in the spread of seizures.

Felbamate has been used as an adjunctive medication for focal seizures and Lennox-Gastaut syndrome in children. The medication is approved as an adjunctive or monotherapy agent for JME and focal seizures (with and without bilateral evolution) but is more often used as second-line treatment for those patients who do not respond adequately to initial treatment [74; 115; 119].

Common side effects include anorexia, headache, insomnia, weight loss, fever, and ataxia. Life-threatening side effects include aplastic anemia, acute liver failure, and Stevens-Johnson syndrome [74; 119]. There have been reports of severe aplastic anemia associated with the use of felbamate, which have resulted in a decreased use of this medication. Consistent follow-up with a CBC is essential for patients receiving felbamate [74; 105].

Fenfluramine

Fenfluramine is a Schedule IV controlled substance, approved by the FDA in 2020 for the treatment of seizures associated with Dravet syndrome [121]. The effectiveness of fenfluramine for the treatment of seizures associated with Dravet syndrome was demonstrated in two clinical studies in 202 subjects 2 to 18 years of age. The studies measured the change from baseline in the frequency of convulsive seizures. In both studies, subjects treated with fenfluramine had significantly greater reductions in the frequency of convulsive seizures during the trials than subjects who received placebo (inactive treatment). These reductions were seen within 3 to 4 weeks and remained generally consistent over the 14- to 15-week treatment periods [121].

The precise mechanism by which fenfluramine exerts its therapeutic effects is unknown. Fenfluramine and the metabolite, norfenfluramine, exhibit agonist activity at serotonin 5-HT2 receptors. There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine and norfenfluramine, and valvular heart disease and pulmonary arterial hypertension [74].

Fenfluramine carries a boxed warning regarding its association with valvular heart disease and pulmonary arterial hypertension. Patients should have cardiac monitoring with echocardiograms performed prior to treatment, every six months during treatment, and three to six months after treatment is discontinued. Because of the risks, fenfluramine is available only through a restricted drug distribution program, under a risk evaluation and mitigation strategy (REMS) [121].

Gabapentin

Gabapentin, also approved by the FDA in 1993, is indicated as an adjunctive therapy for patients with focal seizures, (with and without bilateral evolution), in those who are older than 3 years of age [74]. The exact mechanism of action is unknown but is believed to be related to a novel binding site on neurons. It has been postulated that its effect may be related to an action involving GABA [74]. Common side effects include somnolence, ataxia, nystagmus, amnesia, mood changes, dizziness, fatigue, and tremor. Idiosyncratic side effects include leukopenia and cardiac anomalies [74]. In general, gabapentin is well tolerated and many side effects decrease within two weeks with continued dosing [115].

Lacosamide

Lacosamide was approved by the FDA in 2008 for adjunctive therapy in the treatment of focal seizures in patients 17 years of age and older [119; 122]. The exact mechanism of action remains unknown; however, in vitro studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels [74; 122; 123; 124]. Common side effects include dizziness, diplopia, headache, ataxia, and blurred vision. Idiosyncratic effects include multi-organ hypersensitivity reactions and syncope. Adjunctive use of carbamazepine, phenobarbital, or phenytoin may decrease the serum concentration of lacosamide [74; 122]. As with all AEDs, lacosamide should be withdrawn gradually (over a minimum of one week) to minimize the potential of increased seizure frequency. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [124].

Lamotrigine

Lamotrigine was approved by the FDA in 1994 and has become known as a broad-spectrum AED. The exact mechanism of action of lamotrigine is unknown. However, it is believed to block calcium and sodium channels and stabilize nerve cell membranes [74].

Lamotrigine is approved as an adjunctive therapy for focal seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients older than 2 years of age [74]. The medication is approved for conversion to monotherapy for focal seizures in patients who are older than 16 years of age (immediate release) and 13 years of age (extended release) [74]. Research has reported that this drug is effective across the complete range of seizure types, including focal seizures, generalized seizures of unknown cause, and Lennox-Gastaut [115; 125].

This medication should be initiated at a very low dose and titrated upward slowly. A therapeutic dose may take several weeks to achieve, especially if given with valproate. A slow titration decreases the risk of developing a serious rash. Common side effects include GI distress, dizziness, somnolence, headache, visual changes, and ataxia. Life-threatening reactions include disseminated intravascular coagulation, multi-organ failure, and serious cutaneous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis [105]. Lamotrigine may cause dermatologic reactions that require hospitalization or that cause permanent disability or death within the first eight weeks of therapy [74; 119; 126]. Cutaneous reactions have been reported as long as six months after the initiation of drug treatment. Lamotrigine should be discontinued at the first indication of a drug-related rash.

Drug levels have not been definitively established for lamotrigine, but a suggested range is available. Drug interactions are common with carbamazepine, phenobarbital, phenytoin, primidone, and valproate [74].

Levetiracetam

The indication for this medication, which was approved in 1999, is for adjunctive therapy of focal, myoclonic, and primary generalized tonic-clonic seizures in adults and adolescents and focal and primary generalized tonic-clonic seizures in children. The exact mechanism of levetiracetam is unknown [74; 119]. Frequent side effects include somnolence, difficulty with coordination, and dizziness. Side effects most commonly occur during the first four weeks of treatment [74]. There has been no significant interaction reported with the co-administration of other AEDs. This drug should not be discontinued abruptly due to the risk of increased seizures, unless warranted by severe side effects [74; 115]. Its benefit is still being evaluated.

Lorazepam

Lorazepam is another traditional benzodiazepine that has been used in the treatment of uncontrolled seizures and status epilepticus. It may be administered intravenously or intramuscularly deep into a muscle mass, if necessary, for status epilepticus; oral administration is used for refractory focal seizures [74]. The mechanism of action is similar to diazepam, clonazepam, and the other medications in this class of drug. As with diazepam, lorazepam is typically reserved for emergency situations and is not utilized for the chronic treatment of seizures. Common side effects include respiratory depression, hypotension, and CNS depression [74].

Midazolam

This benzodiazepine has several possible side effects, including severe respiratory depression, respiratory arrest, or apnea. It should be used with extreme caution, particularly in noncritical care settings. Appropriate resuscitative equipment and qualified personnel should be available for administration and monitoring [74; 119]. Labeled uses include preoperative sedation, moderate sedation prior to diagnostic or radiographic procedures, intensive care unit sedation (continuous infusion), and induction and maintenance of general anesthesia. The use of midazolam in the treatment of seizures and status epilepticus is investigational [74].

Oxcarbazepine

Oxcarbazepine was approved in 2000 and is indicated as monotherapy and adjunctive treatment in patients as young as 4 years of age with focal seizures; it can be used as adjunctive therapy in patients older than 2 years of age [74]. It is an analog of carbamazepine and was designed to be similar in effect but to have fewer adverse effects. Primary side effects include dizziness, nausea, headache, somnolence, diarrhea, vomiting, upper respiratory tract infections, constipation, dyspepsia, ataxia, and nervousness. Significant hyponatremia may occur. Serum sodium monitoring may be needed. Precautions should be taken with patients allergic to carbamazepine due to similarities in the drugs' structures [74].

Perampanel

In 2018, the FDA approved a new indication for perampanel to include focal seizures in patients 4 years of age and older. This approval was based on the interim results of a phase III clinical study as well as the results from a phase II clinical study in pediatric patients with epilepsy. Both studies confirmed that the safety and efficacy of perampanel were similar between adult and pediatric patients [127].

Perampanel is a noncompetitive AMPA glutamate receptor antagonist. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurologic disorders caused by neuronal over excitation. The precise mechanism by which perampanel exerts its antiepileptic effects in humans is unknown. Perampanel is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. It is extensively metabolized via primary oxidation and sequential glucuronidation. Oxidative metabolism is primarily mediated by CYP3A4/5 and to a lesser extent by CYP1A2 and CYP2B6 [74].

Serious or life-threatening psychiatric and behavior adverse reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats, have been reported in patients taking perampanel [74].

Phenobarbital

Phenobarbital has been used for the treatment of seizures since the early 1900s. Barbiturates, as a class of drugs, contain anticonvulsant properties. Phenobarbital and primidone are the most commonly used barbiturates; other barbiturates are usually not used due to the sedative and hypnotic effects. The exact mechanism of action is unknown, but phenobarbital elevates the seizure threshold and prevents the continuation of seizure activity. Phenobarbital may assist in the action of certain inhibitory neurotransmitters and repress the action of some of the excitatory agents. Phenobarbital is useful for the management of tonic-clonic, status epilepticus, and focal seizures [74].

This medication is usually tolerated well and may be initiated at the maintenance therapy dose, or alternatively, a loading dose may be administered. The maintenance dose is often taken at bedtime due to the sedative effect of the medication [128]. The primary side effects of phenobarbital are sedation, dizziness, cognitive impairment, and ataxia. The sedative effect may lessen over several weeks of therapy. It has been accepted that phenobarbital has a negative effect on cognitive function and behavior. Some patients may experience idiosyncratic hyperactivity [74]. A rare, but serious, adverse effect is a rash that may progress to Stevens-Johnson syndrome [129].

As with many of the AEDs, drug interactions are common. Phenobarbital drug levels and monitoring for clinical alterations are essential when combining this medication with the other AEDs or other drugs.

Phenytoin

Phenytoin is used for the management of generalized tonic-clonic and certain types of focal seizures. It is also used as an antiarrhythmic agent [74; 119]. The mechanism of action of phenytoin is the reduction of voltage and spread of electrical discharges in the motor cortex by altering ion, sodium, and calcium transport [119]. The most common side effects are usually dose-related and include nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion [119]. There are idiosyncratic adverse effects associated with phenytoin, including gingival hyperplasia and hirsutism, which make this medication a poor choice for female patients. A life-threatening adverse reaction associated with phenytoin is the possibility of Stevens-Johnson syndrome [74].

Phenytoin has a narrow therapeutic margin, and levels of the drug must be periodically monitored. Phenytoin is approximately 90% bound to plasma proteins [74]. The unbound portion, or free drug, is the component that exerts the therapeutic and toxic effects. Certain situations that reduce plasma protein binding, such as renal failure, may increase the free fraction [74]. Blood levels of the bound and unbound (free) levels may be necessary to interpret the total phenytoin concentration with the patient's clinical status.

There are many drug interactions with phenytoin. Therefore, care should be used with other medications, including oral contraceptives, and all prescribing practitioners should be aware that the patient is taking phenytoin [74].

The intravenous form of phenytoin should be given with normal saline because a solution containing dextrose will cause a precipitation. Hypotension is an adverse effect with phenytoin, and the medication should be given via a slow infusion [74]. A related medication is a parenteral form of phenytoin called fosphenytoin sodium. Fosphenytoin is a rapid-acting form of phenytoin that may be administered intravenously or intramuscularly. Fosphenytoin is indicated for the treatment of status epilepticus, as a substitute for phenytoin, and it may be utilized during neurosurgery. Dosing is based on phenytoin equivalents [74].

Pregabalin

In 2004, the FDA approved pregabalin as adjunctive therapy for adult patients with focal seizures. It has structural similarities to GABA but does not appear to mimic its functional properties. This medication binds to a subunit of calcium channels in the brain, preventing the neurotransmitter release associated with a seizure event [74]. Therefore, pregabalin tends to decrease the frequency of seizures when added to an AED regimen. Common side effects include dizziness, somnolence, ataxia, and blurred vision. Possible life-threatening reactions include anemia, heart failure, and Stevens-Johnson syndrome. Adverse effects may be dose-dependent or related to interactions with other medications [74]. However, studies have found no interactions with carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, or topiramate [130]. Pregabalin should not be immediately discontinued, but rather diminished gradually, due to a risk of increased seizure activity. The dosage should be tapered off over a period of at least one week [74].

Primidone

The chemical structure of primidone is similar to that of barbiturates. The two primary metabolites of primidone are phenobarbital and phenylethylmalonamide (PEMA). It is primarily used as an adjunctive treatment and is effective in patients with focal and generalized tonic-clonic seizures [74]. Primidone is initiated at a low dose followed by incremental increases to prevent common GI and sedative effects. Laboratory monitoring should include primidone and phenobarbital levels [74]. Adverse effects are similar to those for phenobarbital. Primary differences regarding primidone include neurotoxicity with long-term therapy and decreased libido. Serious adverse reactions are rare. Drug interactions are common with AEDs and other medications. If primidone is to be discontinued, it should be tapered slowly to avoid rebound seizures or other negative effects [74].

Rufinamide

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. The results of in vitro studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide is extensively metabolized but has no active metabolites. Rufinamide is a weak inhibitor of CYP2E1. It did not show significant inhibition of other CYP enzymes. Monitor patients for signs and symptoms of suicide ideation [74].

Stiripentol

In 2018, the FDA approved stiripentol for adjunctive treatment of Dravet syndrome in combination with clobazam [74]. The precise mechanism behind antiseizure effects is unknown. Stiripentol may enhance GABAergic inhibitory neurotransmission by weak partial agonism and/or positive allosteric modulation of GABA-A receptors. The agent also inhibits multiple cytochrome P450 isoenzymes involved in the metabolism of other antiseizure medications; concurrent use may increase their systemic exposure and efficacy. Prior to initiation of therapy with stiripentol, obtain CBC, renal function tests, and

liver function tests. Monitor weight and growth rate in children. Assess for signs of CNS depression and suicidal ideation [74].

Tiagabine

Tiagabine was introduced into clinical use in 1997 and is indicated as an adjunctive treatment for patients with focal seizures who are 12 years of age or older [74]. Clinical trials have shown that the drug has modest efficacy for focal seizures. The precise mechanism of action is unknown, but tiagabine is believed to enhance the inhibitory neurotransmitter GABA by blocking its reuptake into neurons and glial cells [74; 119]. Common side effects include difficulty with concentration, dizziness, nervousness, somnolence, and tremor [74; 119]. Idiosyncratic reactions are rare but include generalized weakness and rash [115; 119].

Topiramate

Topiramate is another broad-spectrum AED that has had clinical usage for over a decade. It appears to have multiple mechanisms of action, including sodium and calcium channel blockage, GABA potentiation, and glutamate receptor antagonism [74; 119].

Topiramate is indicated as monotherapy and as adjunctive therapy for patients as young as 2 years of age with focal and generalized tonic-clonic seizures and for seizures associated with Lennox-Gastaut syndrome [119]. The exception is Trokendi XR, which is only approved for patients 6 years of age or older [119]. The medication is initiated at a low dose, then titrated upward slowly. Topiramate may take weeks to achieve a therapeutic level. Common side effects include somnolence, dizziness, ataxia, speech disorders, confusion, visual changes, memory problems, and difficulty with concentration and attention [119]. Idiosyncratic side effects include mood changes and renal calculi [74; 119]. Renal calculi occur in 1.5% of patients, which is two to four times the incidence in the general population [119]. Patients are told to take topiramate with a full glass of water to prevent renal calculi formation [74]. As with many of the AEDs, drug interactions are common [115].

Valproate

Valproate, or valproic acid, has extensive activity for a variety of seizure disorders of both generalized and focal onset. Valproate is efficacious in the management of primary generalized tonic-clonic, absence, myoclonic, and focal seizures. The mechanism of action is not entirely known, but the activity of valproate appears to be related to increasing the levels of GABA [74]. As noted, this inhibitory neurotransmitter appears to have properties that help prevent the spread of seizures.

Valproate is available in four forms: Depakene, Depakote, Stavzor, and Depacon [74]. Depakene is available in capsule and syrup form; Depakote is available in delayed-release sprinkle capsule, delayed-release tablet, and 24-hour extended-release tablet forms; Stavzor is available in delayed-release capsule form; and Depacon is an IV solution [74]. Valproate is started with a small dose, then titrated upward to an effective dose.

The primary side effect of valproate is GI upset, including nausea, vomiting, anorexia, and diarrhea [74]. Up to 35% of patients taking Depakene have reported adverse reactions related to the gastrointestinal tract [34; 131]. The incidence of neurologic adverse effects, such as behavioral and cognitive changes, is less with valproate than many of the other AEDs. Idiosyncratic side effects of valproate include tremor, weight gain, and alopecia [74]. Fulminant hepatic failure leading to coma and death is rare but has been reported, especially in children younger than 2 years of age [131]. Liver enzymes should be monitored prior to initiating therapy and periodically during the dosing of this medication [74].

Drug interactions with valproate are common; valproate is believed to inhibit hepatic drug metabolism. Valproate drug levels should be monitored, especially during concomitant use with other AEDs, including phenytoin [74].

Vigabatrin

Vigabatrin is indicated for the treatment of epileptic spasms and refractory focal seizures not controlled by usual treatments. It acts by irreversibly inhibiting GABA-T, thereby increasing the levels of GABA within the brain. The duration of the effect depends upon the rate of GABA-T resynthesis [74]. Common side effects include somnolence, headache, fatigue, and upper respiratory tract infection. An FDA-boxed warning indicates that vigabatrin causes permanent vision loss in infants, children, and adults. Because of this risk and because vigabatrin provides an observable symptomatic benefit when it is effective, patients who fail to show substantial clinical benefit within a short period of time after initiation of treatment (i.e., two to four weeks for epileptic spasms or less than three months in adults) should be withdrawn from therapy [74].

Zonisamide

Zonisamide has been available in the United States since 2000 as adjunctive therapy for patients with focal seizures. Reports suggest this drug may have special benefit for the treatment of myoclonic seizures and is being tested for use in patients with primary generalized tonic-clonic seizures [11]. The medication is approved for patients 16 years of age or older. The exact mechanism of action of zonisamide is unknown, but it is believed to block sodium and calcium channels in the neurons. The most frequent adverse effects include drowsiness, anorexia, and alterations in coordination and thinking [74]. Cytochrome P450 3A4 (CYP3A4) inducers, such as those that are present in carbamazepine and phenobarbital, may decrease the effectiveness of zonisamide [74].

An oral solution of cannabidiol (a cannabis derivative) was approved in 2018 for the treatment of Lennox-Gastaut syndrome. When taken in conjunction with other medications, this drug has been found to reduce the frequency of seizures (compared with placebo) [132]. It may be used in patients 2 years of age and older. Common side effects include sleepiness, elevated liver enzymes, and decreased appetite.

AED Withdrawal

When a patient is seizure-free for more than two years, the patient is considered to be a candidate for AED withdrawal [133]. Patients with generalized seizures and an improved EEG have a more favorable prognosis to remain seizure-free without medications. If the healthcare team and patient agree that this is a viable alternative, a schedule of gradually withdrawing the medications should be considered. The medications may be typically slowly tapered over several months while the patient is closely monitored.

EPILEPSY SURGERY

Although surgical techniques have improved markedly over the past few years, epilepsy surgery is rarely considered a first-line treatment and is usually considered only after years of medication treatment. A surgical approach may be deliberated sooner if the patient's ability to function is hampered by frequent or severe seizures and a specific epileptogenic focus, such as mesial temporal sclerosis, is identified. Surgery for such well-defined syndromes has been shown to yield a better quality of life and reduced anxiety and depression within three months when compared with continued medical therapy [134]. Other focal lesions, including arteriovenous malformations, tumors, and areas of cerebral trauma, have also been successfully resected. The objective of a surgical approach is to obtain a significant decrease in seizure frequency, intensity, or duration with the least sequelae. As a result of new surgical techniques and new ways of identifying affected areas, more of these operations are being done than ever before and with greater success [114].

Intracranial surgery involves inherent risks; however, these risks are less than the risks of uncontrolled seizures. The morbidity and mortality of seizures include accidental injury; cognitive decline; sudden unexplained death in epilepsy (SUDEP); and psychologic, social, and vocational impairment. These factors suggest that continued medical therapy after failure to control seizures with aggressive trials of AEDs is not optimal treatment of certain forms of epilepsy [134].

The precise numbers and type of AEDs to try before recommending surgery remain unknown for the various epilepsy syndromes; however, the AAN, the American Association of Neurological Surgeons, and the AES have recommended the following practice parameters [134]:

- Patients with certain disabling focal seizures ("complex partial seizures"), with or without bilateral evolution, who have failed appropriate trials of first-line AEDs, should be considered for referral to an epilepsy surgery center. (Criteria for failure of drug treatment have not been definitely established.)
- Patients referred to an epilepsy center for the reasons stated above who meet established criteria for an anteromedial temporal lobe resection and who will accept the risks and benefits of this procedure, as opposed to continuing pharmacotherapy, should be offered surgical treatment.

As previously noted, a large percentage of patients continue to experience seizures despite treatment with medications. Studies of patients with new-onset seizures have shown that only 64% have seizure freedom by the time they try their third AED [3]. Thus, after three different AEDs have failed to control seizures, more than 35% of patients continue to have seizures. Therefore, the decision to proceed with surgery should include consideration of both the chance of seizure freedom with additional AED trials and the adverse long-term effects of uncontrolled seizures [134].

While an estimated 60,000 people are candidates for surgery for epilepsy, not all patients are eligible [135]. For example, those with significant medical problems or progressive neurologic disorders are rarely considered surgical candidates. Several diagnostic and prognostic procedures are available to determine an individual's suitability for surgery. The presurgical testing commonly includes the patient's seizure history, a physical examination, laboratory tests, social circumstances, and simultaneous video/EEG monitoring. An MRI, PET, SPECT, neuropsychologic tests, sphenoidal electrodes, and an intracarotid sodium amobarbital test are also commonly used screening methods [134].

Simultaneous video/EEG monitoring may continue for several days to several weeks, depending on the frequency of the patient's seizures. As mentioned, sphenoidal electrodes are inserted through the skin above the jaw and assist with locating seizure activity in the temporal lobe. The goal of this monitoring procedure is to determine the patient's seizure type and location of seizure onset and to evaluate the position of vital areas for speech and memory. It is important to record sufficient numbers of the patient's typical seizures to obtain the most accurate data possible [134]. The patient is kept in a controlled environment in which seizures may occur with consistent monitoring and with the oversight of experienced personnel. The patient's AEDs are usually tapered, and aggravating factors are instituted. Aggravating factors may include sleep deprivation, hyperventilation, or physical exertion.

Neuropsychologic (or neurocognitive) tests analyze a patient's memory, attention, concentration, language, motor skills, intelligence quotient (IQ), and other problem-solving abilities. Epilepsy surgical candidates routinely undergo extensive neuropsychologic testing [134]. These tests are lengthy and may take five or more hours to complete, but they can assist in the localization of a lesion. Testing also gives the healthcare team a better understanding of the patient and how the patient may progress through the surgical process to rehabilitation [134].

The intracarotid sodium amobarbital test, often referred to as the Wada test, combines neuroimaging and neuropsychologic testing methods. The purpose of this test is to determine areas of the brain that are important in speech, thinking, and memory. Although this continues to be a use of the Wada test, functional MRI for language now provides a noninvasive way to more accurately lateralize and localize language functioning [134]. The information derived from the Wada test helps the surgical team determine a proper surgical approach and ascertain any anticipated surgical complications.

The patient is conscious throughout the procedure, during which carotid angiography is performed, usually through a femoral approach. One hemisphere of the brain is anesthetized for several minutes with sodium amobarbital or a similar barbiturate. After the injection, the patient is tested for speech and memory. This consists of reading words, identifying objects or pictures, and answering questions. The patient is then asked to remember what is shown. Arm and hand strength is also tested. The entire side of the body contralateral to the injection site will be momentarily paralyzed. Either one or both sides may be tested in the same manner. A recall of 75% of the items presented during anesthetization is evidence that the contralateral hemisphere should be able to support memory after surgery. Insufficient recall is evidence that the patient may experience significant memory difficulties postoperatively [134]. If additional information is required, a second hospital admission may be necessary for the surgical placement of epidural or subdural electrodes directly onto the surface of the brain. This procedure is generally reserved for the most difficult cases [134]. Depth electrodes, fine wires positioned directly into the deep brain matter, may also be placed. These invasive electrodes are capable of transmitting seizure information that is not detectable by a scalp electrode. While the invasive electrodes are placed, functional mapping may be completed. Functional mapping involves stimulation of the electrodes while the patient is performing certain tasks. These interventions assist in eliciting the seizure focus and determining the involvement of important brain functions [134].

After presurgical testing is complete, further consultations should occur to determine the patient's eligibility for surgery. In this stage, the patient is evaluated to determine the potential benefits versus the risks of a surgical procedure. There are many important questions to consider, such as whether the seizures impair functioning, the severity of the toxicities of the medications, and whether the seizures or the sequelae are harmful to the patient. Finally, the patient's quality of life issues should be addressed.

There are several commonly accepted procedures for the removal of a focal epileptogenic focus. Open surgeries include lobectomy, hemispherectomy, corpus callosotomy, and multiple subpial transection [134]. The use of radiation therapy to ablate the area of abnormality has been increasing in popularity and is available in many medical centers. A linear accelerator, widely known as the gamma knife, is commonly used as a radiation source [136]. The end result of all of these procedures is the interruption of seizure pathways or the removal of the seizure focus.

Lobectomy

The most common type of surgery for epilepsy is removal of a seizure focus. This type of surgery, referred to as a lobectomy, is appropriate only for focal seizures that originate in just one area of the brain. The lobectomy may include removal of all or part of the temporal, frontal, parietal, or occipital lobes. The most commonly performed surgical procedure for epilepsy is a cortical resection, usually of the anterior temporal lobe [134]. Mesial temporal stenosis, identified on MRI, has been successfully treated with a temporal lobectomy [3; 114].

Lobectomies have a 55% to 70% success rate when the type of epilepsy and the seizure focus is well-defined. Temporal lobe resection has been shown to lead to a significant reduction or complete cessation of seizures approximately 70% to 90% of the time [3]. As with any invasive procedure of the brain, infection and edema are potential adverse reactions. Complications from the surgery occur in less than 4% of patients [134].

Hemispherectomy

A hemispherectomy involves disconnecting one hemisphere of the brain from the rest of the brain. This procedure is generally reserved for patients with very severe and frequent seizures that occur unilaterally. It is rarely performed in patients older than 13 years of age [3; 137]. The remaining brain tissue may compensate for the missing hemisphere by gaining additional functions. The negative consequences of the hemispherectomy are residual paresis, loss of some motor function, and visual changes. The

potential risks of this surgery include infection and hemorrhage [134]. Surprisingly, the results of this operation are often reported to be very successful, and the child often maintains excellent seizure control. With intense rehabilitation, the child often recovers nearly normal abilities [3].

Corpus Callosotomy

A corpus callosotomy, or corpus callosum section, splices the innervations between the left and right brain by interrupting the corpus callosum. This type of surgery may be useful for generalized seizures to prohibit the spread of epileptic discharges. Corpus callosotomy is done primarily in children with severe seizures that start in one half of the brain and spread to the other side. Uncontrolled myoclonic, atonic, and tonic-clonic seizures may be reduced in severity or frequency after this procedure [3]. In some patients, generalized seizures may stop while other patients may have a worsening of focal seizures. A 60% to 70% decrease can be expected for more than 80% of patients. Approximately 10% to 15% of patients receive no worthwhile benefit [134]. Complications such as infection, cerebral edema, impaired muscular activity, visual defects, memory, and speech disorders may occur after this type of surgery. The rate of complications has been reported as high as 50%, including several deaths [134].

Multiple Subpial Transection

The most effective surgical treatment of focal seizures has been removal of the seizure-producing cortex from the brain. However, this cannot be performed if the cortex also serves an indispensable function, such as speech. Consequently, multiple subpial transaction (MST) is the only acceptable surgical treatment of a focus within such cortex. MST is a process whereby small incisions are made in the brain to interrupt the spread of seizures without the removal of brain tissue. This may be performed as a single procedure or combined with any of the other surgical methods, including a corpus callosotomy. MST has limited clinical application and is being used less [134]. The results of a Cochrane review found insufficient evidence for the safety and efficacy of MST [138].

Radiation Ablation

Gamma knife radiosurgery has been used for many years for the treatment of cerebral abnormalities. It is available in many large medical centers and university hospitals. One of the primary benefits of the procedure is the elimination of the necessity of a craniotomy, making it essentially a noninvasive procedure [136]. The treatment is often performed in one session with a collimated beam of ionizing radiation focused on the area of abnormality. It can be performed on an outpatient basis, but an overnight stay is recommended. In some centers the results have been comparable to standard surgery for patients with temporal lobe epilepsy, but in others the beneficial results were only short term. This difference may be related to the dose of administered radiation. Side effects have included verbal memory decline, which has been reported to be as high as 60%. However, the technique shows promise, especially in patients with a localized epileptogenic focus and those who cannot tolerate open surgery [136; 139; 140].

Postsurgery Follow-Up

During any surgical procedure for seizures, electrocorticography is completed before the patient leaves the operating room to determine if any EEG abnormalities remain after the resection or alteration of the epileptogenic focus. After surgery, the majority of patients will remain on AEDs for one to two years. Patients should be counseled that the first one to two years after the surgical procedure is a crucial time period to avoid seizure activity. Continuing AEDs is essential in providing the most beneficial long-term outcomes [134].

ELECTRICAL STIMULATORS

The vagus nerve stimulator, first approved by the FDA in 1997, was the first successful medical device for patients with uncontrolled focal seizures [3]. Jacob Zabara, a biophysicist, discovered that breathing techniques could stimulate the vagus nerve and decrease muscular contractions in the abdomen. Because the vagus nerve has an effect on the brainstem, hypothalamus, hippocampus, and amygdala, as well as innervating several organs, Zabara postulated that vagus stimulation could decrease seizures [141].

The stimulator is an implanted device, similar to a cardiac pacemaker, that is connected to the vagus nerve in the neck and stimulates the nerve with electrical impulses. The device is programmed to send electrical discharges at specific intervals automatically and periodically throughout the day [3]. The device is adjusted according to each patient's individual requirements and tolerance. The stimulator can be programmed externally by the attending physician or controlled, if necessary, by the patient with the use of a handheld magnet.

On average, this stimulation reduces seizures by approximately 20% to 40%. Patients usually cannot stop taking epilepsy medication because of the stimulator, but they often experience fewer seizures and they may be able to reduce the dose of their medication [3]. Not all patients are candidates for the device, and the device is approved for use in adults and adolescents only. The stimulator is used as an adjunctive therapy to medications and surgery, not as a first-line consideration. The most common adverse effects reported are hoarseness, alterations in speech, ear pain, cough, shortness of breath, nausea, and throat discomfort. Adjusting the amount of stimulation may eliminate most side effects, although the hoarseness typically persists [3]. Most patients consider the adverse effects to be tolerable.

The responsive neurostimulation (RNS) system is an adjunctive treatment for refractory epilepsy. It received FDA approval in 2013 for adults 18 years of age and older; in 2017, this was expanded to include patients 4 years of age and older [3; 142 ; 181]. The RNS is an implanted device that records and analyzes the patient's EEG and applies targeted stimulation (e.g., electrical stimulation, fast-acting drug) to prevent the seizure from occurring [3; 143; 144]. Controlled clinical trials have demonstrated that the RNS system reduces the frequency of disabling seizures, is well tolerated, and acceptably safe [145].

Deep brain stimulation (DBS) is the direct implantation of electrical stimulators in the basal ganglia (e.g., anterior thalamic nuclei) or the hippocampus in an attempt to control seizures in patients with refractory epilepsy. This treatment is FDA approved for use in various disorders, including essential tremor, dystonia, Parkinson disease, and obsessive-compulsive disorder. In 2018, the Medtronic DBS system received FDA approval to expand the indications to include use in adults with medically refractory focal epilepsy. The DBS system has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to DBS implant (with no more than 30 days between seizures). The system has not been evaluated in patients with less frequent seizures [143; 146; 147; 148]. Serious adverse effects include brain hemorrhage, paresthesias, surgical site infection, and implant site pain [144]. DBS also is approved for refractory epilepsy in Europe, Canada, Australia, and Taiwan, and several trials have shown that the treatment is effective for patients with pharmacoresistant epilepsy (50% to 70% reduction of seizures, and 10% of patients seizure-free after several years) [144]. In 2020, the FDA approved a "new-era" DBS device called Percept. This device can chronically capture and record brain signals while delivering therapy to patients [149].

Researchers are also studying whether transcranial magnetic stimulation (TMS), a procedure that uses a strong magnet held outside the head to influence brain activity, may reduce seizures. In addition, work is being done on a device that can analyze an EEG and automatically deliver a dose of an AED in time to abort a seizure [3; 114].

TREATMENT OF PSYCHOGENIC PSEUDOSEIZURES

Psychologic interventions are important for the patient with psychogenic pseudoseizures. Patients will require counseling and support throughout this process. Psychogenic pseudoseizures often develop as a defense mechanism in response to difficult situations. If this coping strategy is challenged, patients may feel depressed, angry, and vulnerable. Extreme sensitivity and caution are required to achieve a positive outcome for the patient [64].

Prior to a definitive diagnosis, patients may be prescribed AEDs. The medication may continue until psychologic counseling is instituted, after which they are tapered off. A firm schedule of follow-up visits should be established. While the diagnosis of psychogenic pseudoseizures is as real as a diagnosis of epileptic seizures, the etiology, pathophysiology, and treatment are very different. Patients who have documented epileptic seizures may concurrently have psychogenic pseudoseizures. These patients will require psychologic intervention as well as care for the epilepsy [64].

ALTERNATIVE THERAPY

Patients and families often seek alternative treatments in order to manage epilepsy naturally or if other treatment methods have been unsuccessful. The ketogenic diet is an alternative approach to standard medications and epilepsy care. It has been so widely recommended that it is becoming a mainstream form of therapy. Some assertions in the lay literature have suggested that vitamin E and selenium are helpful for some kinds of seizures; however, these claims have not been supported by scientific research.

Ketogenic Diet

The theory behind the ketogenic diet is that it has the same effect on the body as fasting; that is, the body is forced to utilize fat as energy instead of glucose. This can increase ketosis, with a subsequent rise in serum ketones [3; 150].

In the 1920s, this diet was studied as a treatment for patients with intractable epilepsy. As newer medications were discovered, the diet became perceived as a less favorable treatment option. Today, there are many respected centers located throughout the United States that prescribe and monitor the ketogenic diet as a complementary approach to standard AEDs [150; 151]. If a patient's seizures are not controlled on usual medications or if the adverse effects of medications are numerous, the ketogenic diet may be considered. This diet should be prescribed and monitored by a physician in collaboration with a nutritionist [150].

This diet is high in fat, very low in carbohydrates, and low in protein, and fluids are restricted. The usual ratio is three to four parts fat to one part protein and carbohydrates. The diet is nutritionally very inadequate, and children will require vitamin and mineral supplementation. The diet is usually not recommended for adults, as the restricted food choices are difficult to follow [150]. The diet is said to be helpful in tonic-clonic, myoclonic, certain types of focal seizures. Focal motor and myoclonic seizures respond to the ketogenic diet with the most success. Some children find it hard to tolerate, but many do well. Research has indicated that of every three children who begin the diet, one will achieve seizure freedom, or close to it, one will have fewer seizures than before, and one will not benefit from the diet. Some children with excellent results may be able to slowly discontinue medication; however, other children will continue to need some medication in addition to the diet [150]. The most common side effects are constipation, acidosis, and poor weight gain. Less common side effects, generally occurring in 1 in 20 children, include poor linear growth, hypercholesterolemia, kidney stones, and GI upset [150; 152].

Other Alternative Regimens

A cause of concern among physicians is that complementary and alternative medical therapies are often tried by patients with epilepsy without physician knowledge [153]. Herbal medication, with often-undisclosed formulation components, such as heavy metals or steroids, may actually be neurotoxic and could promote seizures [153; 154; 155]. Patients should be warned of this risk, advised to discuss the use of herbal medications with physicians, and cautioned regarding possible drug-herb interactions.

Certain forms of reflex epilepsy are responsive to complementary or behavioral techniques. Epilepsy caused by flashing lights, reading, or hearing certain sounds may be responsive to techniques such as biofeedback. As research continues in these areas, patients may have a more comprehensive and holistic range of treatment options in the future.

PROGNOSIS

Most individuals who develop epilepsy have a high likelihood of achieving resolution. Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but who are past the applicable age, or those who have remained seizure-free for 10 years, with no seizure medications for at least the last 5 years [5]. Frequency, type, and number of seizures are important predictors of outcome [156]. Approximately 60% of patients with epilepsy will achieve a remission during the first year of therapy [157]. Another 15% will achieve a remission at a later time, after treatments have been instituted for a number of years. The remaining 25% will develop intractable epilepsy despite treatment. Patients with underlying neurologic disorders, such as multiple sclerosis and cerebrovascular disease, tend to have epilepsy that is more difficult to control. Patients should continue with regular office visits because seizure disorders may change with age in an unpredictable manner. Some seizures may be outgrown, while others worsen with time. Some patients improve for a period of years and then worsen. It is hoped that some of the newer modalities, including surgery and electrical stimulators, will have a synergistic effect with the AEDs and improve prognosis.

MANAGING AN ACTIVE SEIZURE

There are many misleading and inappropriate concepts about how to care for a person who is having a seizure. It is important for all healthcare professionals to know the basic tenets of care and to teach as many people as possible the proper way to handle a patient having a seizure.

The first rule is to "do no harm." Many individuals witnessing a seizure will try to restrict movement or otherwise restrain the patient. This may cause more harm than good. Bystanders and professionals are encouraged to simply take steps to keep the person safe [158]. For a person who is having a focal or nonconvulsive seizure, this merely requires guiding the individual away from a source of danger, such as a busy highway, steep stairway, or hot stove. In general, it is best to gently guide the person, as grabbing or holding may cause a struggle and aggravate the situation. Speak to the individual in a calm and reassuring way, and stay with him or her until the episode is over, especially if there is a period of unconsciousness [158].

When assisting a person who is having a generalized tonic-clonic seizure, it is vital to remember to keep calm and reassure others in the vicinity that there is no need to interfere. However, bystanders can assist in removing any sharp or dangerous objects in the immediate area. Loosening a patient's tie or any other object that may cause impairment to respiration may also be helpful. Removing loose dentures or food that is expelled from the mouth has been recommended, but forceful removal or shoving an object into the mouth may cause injury and is contraindicated [158]. Placing something soft and flat under the individual's head may prevent an injury, and turning the victim gently onto his or her side can help to clear the airway and avoid aspiration. There is no need for artificial respiration except in the very rare cases when respiration ceases and does not resume after the seizure ends. If in a care center, supplemental oxygen should be available and provided if indicated. The individual should not be left alone until the seizure ends naturally. One should be prepared to offer assistance to a possibly confused or somnolent postictal individual when the seizure activity ceases [158].

Timing the length of the seizure can provide useful information for the patient's future management. It would also be helpful to assess the patient's breathing and determine if there are any apneic periods [158].

COMPLICATIONS OF SEIZURES

Complications from seizures are varied and numerous. Patients can sustain injuries, both physical and neurologic. A patient with any type of seizure may sustain a physical injury, especially during impaired consciousness. Patients may experience abrasions, bruises, broken bones, burns, and oral lacerations, including tongue and cheek injuries. Other patients may experience a severe head injury or other trauma with sudden falls to the floor or falls from heights [3; 38].

During a seizure, there is an increase in metabolic requirements associated with heightened cerebral oxygen consumption, glucose consumption, and cerebral blood flow [159]. Animal studies have shown that the repetitive discharge from an epileptic focus produces long-lasting and permanent changes in neuron excitability in local and distant areas of the brain. These studies suggest that the initial seizure may cause additional seizures to occur and can cause secondary brain injury [40; 41; 42]. The longer patients continue without good seizure control the more difficult the seizures are to manage.

Patients may also develop complications due to AEDs. Adverse drug reactions and idiopathic and life-threatening reactions are possible with these medications. Some adverse reactions are related to the dose, while others might occur without toxicities [155].

STATUS EPILEPTICUS

Status epilepticus, or status, is defined as uninterrupted seizure activity or frequent succession of seizure activity. The time variable for status varies greatly depending upon the sources cited. In general, a patient is considered to be in status if a single seizure continues for more than 15 minutes or if there is a rapid succession of seizures lasting more than 30 minutes. Statistics support the notion that after about 30 minutes of seizures, mortality takes a robust leap [160; 161]. However, the Epilepsy Foundation has advised that parents and the public call for emergency assistance when a convulsion continues for more than five minutes without stopping. The Foundation's Working Group on Status Epilepticus has recommended that emergency room physicians treat as status epilepticus if seizure activity has continued for more than five minutes [161; 162; 163].

Convulsive status epilepticus involves tonic-clonic seizures and is a medical emergency [161]. An estimated 55,000 deaths and thousands more instances of brain damage per year follow episodes of status [162]. The majority of these episodes occur in people who do not have epilepsy but have other acute medical illnesses, such as brain tumors or infections, craniocerebral trauma, or cerebrovascular disease. Ingestion of cocaine or other illegal drugs and toxic or metabolic disorders may also trigger a status episode.

Nonconvulsive refers to absence or long or repeated absence or focal impaired awareness seizures. Nonconvulsive status can present in various ways, including loss of speech, automatisms, and alteration of consciousness [161]. Nonconvulsive status seizures are harder to recognize than convulsive status seizures. Symptoms are more subtle, and distinguishing seizure symptoms from the recovery period is difficult [161]. While not generally viewed as being as damaging as convulsive status, nonconvulsive status involves repeated excessive electrical discharges in the brain and should also receive prompt treatment [162]. The most dangerous form is the tonic-clonic type. Cerebral complications occur from high metabolic demands, changes in calcium influx, brain edema, acidosis, hyperthermia, hypoglycemia, hypotension, prolonged autonomic dysfunction, hypoxia, arrhythmia, acidemia, aspiration, and ultimately, brain damage.

In 2016, the American Epilepsy Society (AES) issued new guidelines for the treatment of status epilepticus, which provide a time-dependent treatment algorithm consisting of four phases [164]. The first or "stabilization phase" occurs in the first five minutes of seizure activity and includes standard initial first aid interventions for seizures [164]. As with any emergency situation, the first priority is the

maintenance of a clear airway. The patient sustains a rapid depletion of oxygen and other nutrients during status. Often, the individual is intubated to assist with oxygenation and the prevention of aspiration. The patient will usually require supplemental oxygen. Continuous assessment of all vital functions and neurologic status is necessary. Cardiac monitoring is required to identify dysrhythmias and to allow for appropriate intervention. The patient should be protected from injury and provided a safe environment with close supervision. Laboratory evaluations should be completed to assess AED levels and to check for any metabolic changes. The patient may require additional glucose, which is administered intravenously, to meet increased metabolic requirements. AEDs may be prescribed for intravenous injection and infusion [84; 161; 164].

Interventions for the initial therapy phase (minutes 5 to 20 of seizure activity) include a benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam). Although use of IM midazolam for status epilepticus is off-label, the AES guideline recommends it as the drug of choice when IM administration is necessary for emergent control [74; 164]. Diazepam was once considered the drug of choice for the immediate treatment of status epilepticus; however, lorazepam has emerged as the preferred benzodiazepine for acute management of status epilepticus [84; 164; 165]. Lorazepam is less lipid-soluble than diazepam, with a distribution half-life of two to three hours versus 15 minutes for diazepam, providing a longer duration of clinical effect [165]. The anticonvulsant effects of lorazepam last 6 to 12 hours, and the typical dose ranges from 4 – 8 mg. This agent also has a broad spectrum of efficacy, terminating seizures in 75% to 80% of cases. Its primary adverse effect (respiratory depression) is identical to that of diazepam [84].

Interventions for the second therapy phase (20 to 40 minutes) include valproic acid, levetiracetam, and fosphenytoin. IV phenobarbital is a reasonable alternative if none of these recommended therapies are available [164]. Use of both valproic acid and levetiracetam for status epilepticus is off-label. However, the AES guideline recommends they be considered for use in urgent control of status epilepticus in adults [74; 164].

Phenytoin is one of the most effective drugs for treating acute seizures and status epilepticus. The main advantage of phenytoin is the lack of a sedating effect. However, a number of potentially serious adverse effects, such as arrhythmias and hypotension, may occur. These effects may be associated with a more rapid rate of administration and the propylene glycol vehicle used as its diluent. In addition, local irritation, phlebitis, and dizziness may accompany intravenous administration [84].

Fosphenytoin was approved by the FDA in 1986 for treatment of status epilepticus. It is converted to phenytoin within 8 to 15 minutes. It is metabolized by the liver and has a half-life of 14 hours. It may be infused at a rate three times faster than that of intravenous phenytoin. However, adverse effects unique to fosphenytoin include perineal paresthesias and pruritus, both related to the higher rates of administration [74]. Although fosphenytoin represents an improvement over traditional phenytoin, it is expensive and some hospital formulary committees are unwilling to pay the difference [84]. Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative [164].

The third therapy phase begins when seizure duration reaches 40 minutes (40 to 60 minutes). Although the AES guideline indicates that "there is no clear evidence to guide therapy in this phase," treatment considerations should include repeating second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring) [164].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Emergency Physicians recommends the administration of an additional antiepileptic medication in patients with refractory status epilepticus who have failed treatment with benzodiazepines.

(https://www.acep.org/globalassets/new-pdfs/clinical-policies/seizures-2014-final.pdf. Last accessed September 28, 2022.)

Strength of Recommendation: A (Generally accepted principles for patient care that reflect a high degree of clinical certainty)

The patient's family members will require support and education during this time. When the patient is stabilized, the family members may be helpful in assessing the cause of the patient's status epilepticus and in finding solutions for the prevention of future events. The most prevalent cause of status epilepticus in epileptic patients is failure to comply with AEDs [162].

MORTALITY AND SUDDEN DEATH

Patients with epilepsy have a mortality rate that is higher than the average population. Mortality may occur due to the etiology of epilepsy, which may include a malignant brain mass or a genetic abnormality. Death can also result from a seizure or a complication of a seizure. As noted, patients who develop status epilepticus may not recover. Other patients may have serious injuries or accidents that may lead to death, including falls or burns.

The most common epilepsy-related category of death is SUDEP, accounting for up to one-fifth of epilepsy deaths. SUDEP seems to occur more commonly during sleep, and it preferentially affects young adults with medically intractable epilepsy (especially tonic-clonic seizures). The bulk of evidence supports the concept that patients with uncontrolled seizures are at greatest risk for SUDEP. High seizure frequency and polytherapy also seem to be risk factors. Evidence for many other risk factors is conflicting. The most commonly suggested mechanisms for SUDEP are cardiac abnormalities and apnea, but the cause of SUDEP remains unknown [166; 167; 168].

PATIENT EDUCATION

Epilepsy is a chronic disorder and often requires long-term management. The patient and family should be encouraged to obtain information about epilepsy through self-education. Local epilepsy organizations often provide written materials and information via other media. Frequently, the patient's family members or other significant persons require as much education as the patient because they will be observing the patient during the actual events. These significant persons should be educated to care for the patient during and after a seizure. They should be instructed to stay with the patient until he or she is conscious, time the seizure duration, and provide for the patient's safety. If consciousness returns without further incident and the seizure ends in less than five minutes, then the convulsion is considered to be uncomplicated and emergency attention is not necessary. In general, after a period of rest, the patient is able to resume caring for him or herself [158]. The spouse or other significant person is a crucial asset for the patient and can assist in differentiating between an emergency and an uncomplicated seizure, even though, to the general public, all seizures may appear to be emergencies. The assisting person is important in the prevention of injury and can also help the patient maintain an accurate seizure calendar and ensure medications are taken appropriately.

An ambulance should be called if a seizure lasts longer than five minutes or if seizures continue to reoccur without the patient regaining consciousness. Other situations when emergency assistance is required include seizures that [158]:

- Occur in water, due to likelihood of cardiac or pulmonary damage
- Have related signs of injury
- Result in physical distress
- Occur in patients with diabetes
- Arise in a pregnant patient
- Are the first seizure in a patient without epilepsy or if the health history is unknown

If consciousness does not return after the seizure appears to be over, then emergency assistance will also be required.

As previously described, the Epilepsy Foundation has basic suggestions for caring for a person who has a seizure. These should be related to first responders and those who may be present when a seizure occurs [158].

Patients with a seizure disorder should wear identification wristbands or necklaces. These items are helpful in situations in which a seizure occurs in public. Identification jewelry acts to alert bystanders and healthcare personnel regarding the patient's medical condition and appropriate treatment. Identification is also important to prevent unnecessary or inappropriate interventions, such as the initiation of cardiopulmonary resuscitation. Additional information may also be carried by the patient, including the name and telephone number of healthcare providers, types of medications, and known allergies [169].

On an individual basis, a significant other may be requested to administer medications, such as rectal diazepam or oral lorazepam. Therefore, these individuals will require education regarding multiple aspects of patient care and seizure control. Often, the significant other will require emotional and psychologic support [169]. Watching any person, especially a loved one, having a seizure can be a terrifying and stressful experience.

Teaching patients about their medications is essential. AEDs and other medications should be taken regularly and continuously. Some patients may require medications for a lifetime, and they should be informed of this possibility. The patient should receive information about the name and type of the medication, the dose and schedule of administration, potential side effects, and when to call healthcare providers. For most patients, a written schedule and pillbox are helpful. The patient should also be aware of the appropriate action to take if a dose is missed. Many persons taking AEDs require therapeutic drug monitoring of the drug levels as well as blood tests for other laboratory values. Patients should be informed of the necessity and frequency of laboratory monitoring [3; 111; 170].

Some individuals are susceptible to a seizure that is provoked by a simple sensory experience. The most common sensations are flashing lights or shifting patterns. Sleep deprivation and sudden noises are other precipitating factors. The susceptibility to these phenomena is most commonly noted in the generalized epilepsies of childhood but may occur in all epileptic seizure types. Patients should be told to avoid situations in which these provoking factors may be present [35]. Those who are sensitive to flashing lights should avoid driving, especially at night, as light flickering through trees or fence posts may precipitate a seizure event. Very rarely, seizures are elicited by more complex situations, such as from music or when doing mental calculations.

In addition to the education of patients and their families, other individuals may require knowledge that would enable them to provide the best quality of life for the patient. The education of teachers and/or coworkers may enhance the care of the epileptic person by providing a supportive and safe environment. These individuals should be aware of appropriate interventions and telephone numbers should a seizure event arise. The patient or healthcare providers, upon the patient's request, may contact other significant individuals. Patients may also require support in everyday situations; for example, a bus driver having knowledge of a patient's condition can ensure the patient's safety during the bus ride [3; 158].

SAFETY EDUCATION

Injuries are the primary complication of seizures. Patients with epilepsy often cause harm to themselves by biting their tongues or falling down and hitting a piece of furniture. As noted, the patient should be safeguarded from injuries and falls. Injury prevention is a key aspect of patient education and the maintenance of quality of life. The patient and family should be instructed on constructive methods of safety planning without being overburdened with unnecessary restraints and concern. If possible, the environment should be altered during a seizure rather than restraining the patient. A helmet may be a reliable alternative to provide a protective environment [171].

At home, the patient should evaluate the living situation. General household safety precautions include applying thick carpeting, padding sharp objects, avoiding lighting of fires, and obtaining automatic shut off switches for space heaters, curling irons, and irons. The patient should be informed that smoking is not recommended and certainly not permitted in bed. Bathroom safety measures include setting the water temperature below 120 degrees, using a handheld shower while seated in the bathtub, installing padded carpet in the bathroom, and preventing the bathroom door from locking. The kitchen can be a perilous environment, and cooking can be especially dangerous for the individual who experiences a change in consciousness. Patients should be cautioned about the risk of falling onto a hot stove or leaving the heating elements and oven on. Kitchen safety measures include the use of plastic cups, plates, and cooking utensils, cooking on the back burners of the stove, using a microwave oven, and sliding containers on the counter top rather than picking them up [171].

Recreational activities pose a unique challenge for many active epileptic patients. Most individual sports are considered acceptable, with the exception of scuba diving, parachuting, or activities involving a motorized vehicle. Patients are generally advised that they may participate in basketball and baseball. Football and boxing are often prohibited. If indicated, a mask worn over the face or a helmet may be necessary and helpful during potentially dangerous activities. To improve their safety during recreational activities, patients should consider taking frequent breaks, exercising on soft surfaces, wearing head protection, and always taking along a companion [171].

HEALTH PROMOTION

Health promotion of individuals with epilepsy includes the management and reduction of seizure activity. The patient should be instructed to obtain adequate rest, limit alcohol, reduce stress, eat a healthy diet, and exercise. Patients susceptible to the effects of caffeine and aspartame should avoid these products. These interventions assist in the patient's overall well-being, prevent other disease states, and assist in seizure control [171]. Any precipitating situations that trigger seizure activity, such as flickering lights, should be identified and avoided. An accurate and comprehensive seizure diary may assist with revealing these factors. Patients should also be guided with regard to medication compliance and the necessity of follow-up visits. The patient and family members should be provided with appropriate resources, including information on the local chapters of epilepsy support groups.

PREVENTION OF EPILEPSY

Genetic epilepsies are not preventable. However, there are multiple avenues in which epilepsy can be prevented in the general population [172]. Prevention can occur before birth with improved prenatal care. Folic acid supplementation should occur in women of childbearing age prior to conception to prevent neural tube defects. The current recommended allowance of folic acid for nonpregnant individuals is 0.4 mg/day [173]. During pregnancy, care should be taken to avoid maternal systemic illness and infection, which can affect the developing fetus's CNS. A reduction in the number of early teenage pregnancies may decrease the incidence of premature and/or low-birth-weight infants and maternal infections. Improved perinatal care in the labor and delivery area may also decrease fetal trauma and hypoxia [1; 3; 4; 92; 172].

High fevers in children, especially in those susceptible to seizures, should be monitored and treated appropriately. Parents or caregivers of small children should be instructed in how to take an accurate temperature, based on the child's age. Parents should also be instructed about the significance of a fever and how to intervene when necessary; it is important that they understand when to call a healthcare professional regarding an elevated temperature and when to treat the child with antipyretic medications [4; 27; 77; 172].

The prevention of childhood infection and toxic ingestions is crucial in averting the development of epilepsy. Meningitis, viral encephalitis, measles, mumps, and diphtheria can be minimized through appropriate immunization of children and adults. The prevention of toxic poisonings through screening and safety measures is essential. Lead poisoning continues to be problematic in many older homes [4; 35].

Another area that may minimize the incidence of epilepsy is the reduction of motor vehicle accidents and the prevention of trauma. Traumatic injuries can occur through a variety of accidents and abuse. The utilization of safety belts and restraint devices in all motorized vehicles is essential for children and adults. Settings in which there is a potential for gunshot wounds should also be avoided to prevent the occurrence of head injuries and the subsequent development of epilepsy. Practicing safety during sporting activities is also essential. The prevention of abuse is vital in the reduction of head trauma-related epilepsy. Workplace injuries should be reviewed and reduced. Lastly, the prevention of substance abuse and the use of illicit drugs will assist in the reduction in the incidence of epilepsy [3; 4; 11; 29; 35].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Communication with patients regarding prevention and education is a vital aspect of caring for patients with seizure disorders or epilepsy. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

In a multicultural setting, interpreters are a valuable resource to help bridge the communication and cultural gaps between patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, interpreters serve as cultural brokers who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes.

DRIVING RESTRICTIONS

For individuals with epilepsy, the safe operation of a motor vehicle is a complex issue. The caregiver must try to achieve a balance between providing the best care to the patient and providing the patient with the autonomy and freedom that often coincides with driving. Safety must be the highest priority for the patient and for other individuals. This issue is further complicated by a variety of state statutes and regulations.

A helpful reference concerning driving restrictions in each state is available from the Epilepsy Foundation [174]. Each state has specific requirements for obtaining a driver's license and restrictions for persons with certain medical conditions (***Table 7***). Laws change, however, and each healthcare professional and patient should be aware of the current laws governing the state in which they practice and reside.

CHALLENGES FACING PATIENTS AND THEIR FAMILIES

Patients with epilepsy face unique challenges. For many individuals with epilepsy, a perceived stigma creates diverse psychosocial issues [172; 175; 176]. A seizure may be referred to as a "fit" or an "attack," and there are corresponding bizarre interpretations of this phenomenon. Historically, seizures have been associated with supernatural powers, demonic possession, and insanity [3; 42]. Society places value on self-control, conformity, and independence, all of which may be inhibited by a patient's epilepsy. There is confusion on the part of many individuals when a person has a seizure. Observers and the police may consider the individual drunk, disorderly, or mentally ill. The patient may be institutionalized or jailed.

EXAMPLES OF STATE DRIVING RESTRICTIONS[a]				
State	**Seizure-Free Period**	**Periodic Medical Updates Required**	**Doctors Required to Report**	**DMV Appeal of Denial**
California	Three or six months, with exceptions	At discretion of Department of Motor Vehicles	Yes	Yes
Florida	Six months (or less, at the discretion of physician)	At discretion of medical advisory board	No	Yes
Georgia	Six months	At discretion of medical advisory board	No	Yes
Illinois	No set period	At discretion of medical advisory board	No	Yes
Michigan	Six months, with exceptions	At discretion of Department of Motor Vehicles	No	Yes
New York	One year, or less at discretion of Department of Motor Vehicles	At discretion of Department of Motor Vehicles	No	Yes
Ohio	No set period	At discretion of Department of Motor Vehicles	No	Yes
Pennsylvania	Six months, with exceptions	At discretion of medical advisory board	Yes	Yes
North Carolina	Six months	Annually, or less at discretion of Department of Motor Vehicles	No	Yes
Texas	Three months, with exceptions	At discretion of medical advisory board	No	Yes
[a]Please consult your State Department of Motor Vehicles for more comprehensive information.				
Source: [174]				*Table 7*

Patients with active seizures frequently experience low self-esteem, resulting from perceptions of being less competent and less healthy than others [175; 176]. The unpredictability of seizures, feelings of lack of control and helplessness, and the adverse effects of the medication regimen contribute to a disruption in the patient's sense of well-being [175; 177]. Unfortunately, the majority of these psychologic alterations are not assessed by the general practitioner.

Patients with uncontrolled epilepsy are at greater risk of feelings of anxiety, depression, and stigmatization than those with less frequent seizures [176]. Frequent seizures impact employment and driving, which have a significant effect on self-esteem and feelings of isolation [172]. Unemployment among people with uncontrolled epilepsy has been found to be higher by as much as 50% in developed countries [57; 175]. People with epilepsy have a higher prevalence of learning disabilities and memory problems, often caused by comorbid conditions such as brain damage. Children are exceptionally vulnerable to the negative impact on social and intellectual development. Attention deficits occur during seizures, especially during absence seizures in school-aged children. Children with epilepsy require medical care and AEDs that often affect academic and personal performance. The side effects of AEDs, such as drowsiness and short attention span, may affect educational achievement and are commonly exacerbated by polytherapy [57; 175].

Healthcare personnel can help patients identify people who may be supportive and to whom they may explain the seizures and treatment. They may also help patients focus on positive aspects of life, rather than limitations. Appropriate referrals to an epilepsy specialist nurse, psychologist, psychiatrist, or community worker may be indicated. The community worker can provide support, be an informed and empathetic listener, alleviate fear of the unknown, encourage compliance, and provide information to the patient and the patient's family [175]. The interdisciplinary healthcare team should anticipate and provide solutions for common social issues, difficulty with self-image, frightening experiences, loss of control, and difficulty with independence. Essentially, all members of the team may be vital links to assist each individual to adjust to their personal limitations and difficulties. Lifestyle adjustments should be considered without unnecessarily inhibiting the patient's activities and routines.

EPILEPSY RESEARCH

The Epilepsy Phenome/Genome Project is the largest study ever created to understand how genetics influences epilepsy. Researchers from major epilepsy centers around the United States are collecting blood samples and detailed seizure histories on a group of people with specific types of epilepsy. This information will be used to identify genes that contribute to a person developing epilepsy and the response to seizure medications. The hope is that this information will reveal new insights, improve diagnosis and treatment, and answer many unanswered questions about epilepsy. This study is funded by the National Institute of Neurological Disorders and Stroke (NINDS), a division of the National Institutes of Health [178]. Information gathered from this study is forthcoming.

The AES, Citizens United for Research in Epilepsy, Epilepsy Therapy Project, Finding a Cure for Epilepsy and Seizures, NINDS, and Tuberous Sclerosis Alliance are among the other organizations that are conducting epilepsy research, including pediatric epilepsy, new therapies and treatment modalities, epilepsy education, and seizure prediction [179].

Paradigm-shifting research has begun to alter understanding of the processes by which seizures develop. These new discoveries may lead to new forms of therapy and seizure prediction and potentially to the ability to predict epilepsy [180].

CASE STUDY

Patient R is a woman, 38 years of age, with a history of seizures since birth. She is otherwise in good health. Her current diagnosis is temporal lobe epilepsy. Patient R experiences focal seizures ("complex partial" and focal seizures that evolve bilaterally). She states that she is aware that a seizure is going to occur because she has a very brief "strange sensation." This sensation is her aura. After the aura, the patient cannot recall any other events until the postictal period. During the postictal time, Patient R is fatigued and confused and often experiences headaches.

Witnesses have noticed a typical pattern to Patient R's seizures. First, she becomes very quiet and blank. She will not communicate or respond to other individuals. She experiences vocalizations and yells in a very loud voice, "Jesus, help me." During the vocalizations, Patient R will experience automatisms that include pulling at her clothing. Usually, the seizure ends after approximately 60 seconds, and she regains consciousness within several minutes. At other times, the seizure will evolve, and she will experience tonic posturing followed by clonic movements. The tonic-clonic phase is quite severe and may last several minutes. The postictal period after the evolved seizure is prolonged and may last for several hours. Patient R experiences disorientation, confusion, and somnolence. She has experienced status epilepticus twice in the past.

At times, Patient R's seizures occur almost every day. However, some days will be seizure-free, and she may have several days at a time with no seizure events. Unfortunately, this does not occur consistently. Most days she will experience at least one seizure, and often she has several during the same day.

She has been on a number of AEDs in the past, including phenytoin, phenobarbital, valproic acid, and experimental medications. Her current medications include carbamazepine and topiramate, with lorazepam as needed. She also takes an over-the-counter multivitamin and, occasionally, acetaminophen for headache. Her sister has been instructed on administering lorazepam when Patient R is experiencing several consecutive seizures that occur over a 15-minute period or after her second bilaterally evolved focal seizure for the day. Her sister administers the lorazepam approximately once every two weeks. However, Patient R's seizures are quite variable with no known pattern. One week, she may not require any lorazepam; the next week, she may require it several times.

Patient R is very compliant with her medications. She uses a pillbox and can correctly describe her daily medications and doses. She has used a seizure calendar method of tracking her seizures for years. Each day she records the number of seizures she has and describes them. Patient R has no family history of epilepsy, and she has not had any surgical treatments.

During Patient R's physical examination, her physician discovers that the patient has difficulty with coordination. There are deficits in cognitive processes, such as calculation and abstract thinking. The exam is otherwise unremarkable.

Patient R has a twin sister who is neurologically normal. The twin sister provides a large amount of social and emotional support and is always present to accompany the patient at her visits. Patient R is a very independent woman who lives in an assisted living center and wears a protective helmet. She has completed the 5th grade. She does not use nicotine products, drink alcohol, or use illicit substances. She has experienced difficult situations in the past related to a divorce and loss of her only child.

The patient has been involved in the trial of several new experimental AEDs with varying success. The latest study she participated in had a positive effect on her seizure frequency. Unfortunately, the pharmaceutical company discontinued the medication from the study. As a result, other alternatives were sought. Her current healthcare providers evaluated Patient R and placed her in the epilepsy monitoring unit for simultaneous EEG/video monitoring.

In the epilepsy monitoring unit, Patient R's AEDs are slowly withdrawn. She begins to experience her typical events, including vocalizations. During these events, a large amount of motor activity is exhibited and EEG readings are difficult to ascertain. The medical team suspects a diagnosis of pseudoseizures. The patient completes the neuropsychologic testing, and the evaluation continues for several days. The patient experiences a focal seizure that evolves to a bilateral convulsive seizure, and the EEG readings clearly reveal epileptogenic changes. Sphenoidal electrodes are placed to obtain localizing information. Patient R continues to have a large number of seizures and requires frequent administration of intravenous benzodiazepines to maintain seizure control.

After more than a week of monitoring, a seizure focus is determined. Unfortunately, multiple focal areas exist in the bilateral temporal and frontal lobes, eliminating the surgical option. The patient is restarted on her AEDs and stabilized, and alternative treatments are discussed. The patient and healthcare team agree that a vagus nerve stimulator would be a positive option. Alterations in the medication regimen are discussed. The patient and sister are offered the option to attempt dosing with felbamate with close monitoring. Patient R does not want to attempt felbamate and opts for slowly removing the topiramate and attempting a trial with lamotrigine while awaiting the vagus nerve stimulator placement. This medication is somewhat helpful, but the vagus nerve stimulator provides substantial relief.

CONCLUSION

The impact of seizures and epilepsy on a patient's life is significant. While various forms of seizures and epileptic syndromes exist, there is a degree of anxiety associated with each event. Seizures affect all facets of a patient's life as well as the lives of family members and friends and the communities in which they live.

Medical personnel in all practice settings should understand the potential causes and management of epilepsy and seizure disorders to effectively assist their patients. By providing information, support, treatment options, and community resources, the disorder's negative impact on all involved can be mitigated. Appropriate interventions and care are critical contributions.

The primary goal for all individuals is the prevention of epilepsy. For cases where total prevention is unlikely, the objective is optimal mental and physical functioning despite the disorder. Other objectives include freedom from seizure-induced injury, the achievement of tolerable side effects from AEDs, and satisfactory social and psychologic functioning. Through interventions and education, healthcare professionals can make a positive difference in achieving progress toward these goals.

RESOURCES

American Academy of Neurology
https://www.aan.com

American Association of Neuroscience Nurses
https://aann.org

American Epilepsy Society
https://www.aesnet.org

Centers for Disease Control and PreventionEpilepsy
https://www.cdc.gov/epilepsy

Epilepsy Foundation
https://www.epilepsy.com

International League Against Epilepsy
https://www.ilae.org

National Institute of Neurological Disorders and Stroke (NINDS)Epilepsy Information Page
https://www.ninds.nih.gov/health-information/disorders/epilepsy

National Library of Medicine MedlinePlus/Epilepsy
https://medlineplus.gov/epilepsy.html

American Epilepsy Society Research
https://www.aesnet.org/research-funding/funding/research-funding

Tuberous Sclerosis Alliance
https://www.tsalliance.org

World Health Organization
https://www.who.int/mental_health/neurology/epilepsy

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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