Epilepsy Update, Part 1: Refining Our Understanding of a Complex Disease

Recent findings shed light on the nature of epilepsy, its etiology, and its pathophysiology.

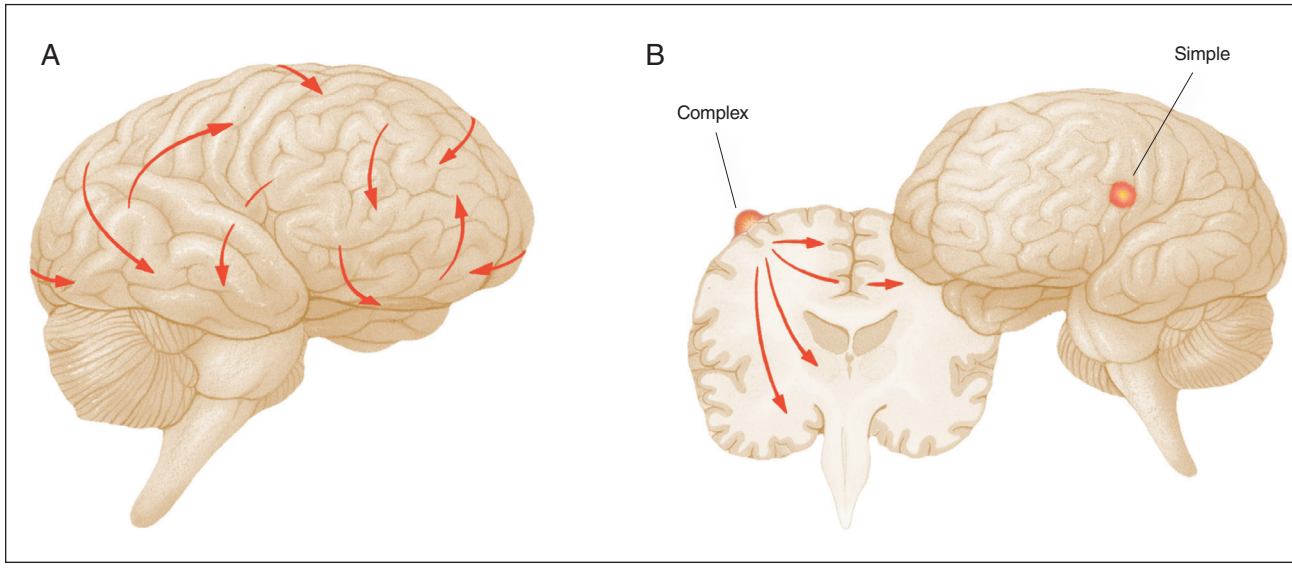
OVERVIEW: Epilepsy is a serious, common neurologic disease that affects people of all ages. As underscored in the 2012 Institute of Medicine report *Epilepsy Across the Spectrum: Promoting Health and Understanding*, the millions of people living with epilepsy in the United States face the challenges of seeking out high-quality, coordinated health care and community services; overcoming epilepsy misinformation and stigma; and finding understanding and support in their communities. This article, the first in a two-part series, discusses new research that has increased our understanding of epilepsy's etiology and pathophysiology, new definitions that are changing the ways we evaluate and treat this disease, conditions that frequently present with epilepsy, and psychosocial challenges faced by people with epilepsy. Part 2, which will appear in next month's issue, reviews comprehensive nursing care and evidence-based treatment for epilepsy and presents resources for people with epilepsy and their families.

Keywords: epilepsy, focal seizure, generalized seizure, seizure, status epilepticus

Every four minutes someone in the United States is diagnosed with epilepsy.[1] The Centers for Disease Control and Prevention estimates that there are about 2.9 million people with epilepsy in the United States.[2] This serious, common neurologic disease affects men and women of all races, ethnicities, and ages, and most often presents in childhood or in older adulthood. Roughly 1.5% of adults ages 65 and older have epilepsy.[3] Prevalence is higher in men than in women, although the difference is minimal in most studies.[4] Few studies have examined racial and ethnic differences in prevalence. Of those that have, a 1986 racially diverse study that included nearly 24,000 Mississippi residents found age-adjusted prevalence to be 8.2 per 1,000 among blacks and 5.4 per 1,000 among whites, though it did not control for socioeconomic status, and a UK medical record review found that the prevalence among South Asians was less than half that of non–South Asians (3.6 versus 7.8 per 1,000).[4]

In terms of disability-adjusted life years, the global disease burden of epilepsy is greater than that of Alzheimer's disease, Parkinson's disease, and multiple sclerosis combined.[5] In the United States, the direct and indirect costs of epilepsy are estimated to be $15.5 billion annually.[2]

Figure 1. Two Types of Epileptic Seizures



Generalized seizures (A) affect both hemispheres of the brain at the same time. Abnormal activity is not focused in one specific area, and there is generally no aura at the start of the seizure. Focal, or partial, seizures (B) originate in one area of one hemisphere, generally in the temporal or frontal lobe. Focal seizures are either simple or complex, depending on whether the person remains fully conscious during the seizure (simple) or consciousness is impaired (complex). Illustration courtesy of the Anatomical Chart Company.

The seizures that characterize epilepsy are unpredictable and frightening. They can interfere with school and work and limit a person's ability to drive or perform other activities of daily living. As many as 40% of patients diagnosed with epilepsy require treatment with more than one antiseizure drug, and those with refractory seizures may need to take three or more drugs in tandem.[6] People with epilepsy are 20 times more likely to die suddenly and unexpectedly than people in the general population; incidence rates of sudden unexpected death in epilepsy (SUDEP) range from 0.9 to 2.3 per 1,000 person-years in the general epilepsy population to 1.1 to 5.9 per 1,000 person-years in people with chronic refractory epilepsy.[7]

The 2012 Institute of Medicine report *Epilepsy Across the Spectrum: Promoting Health and Understanding* identified research priorities for improving surveillance and prevention, health care, health care provider education, quality of life and community resources, patient and family education, and public awareness in order to improve the lives of people with epilepsy and their families.[8] This two-part article highlights some of the report's findings and recommendations, emphasizing those most pertinent to nurses.

NEW DIAGNOSTIC CRITERIA

Epilepsy is a complex spectrum of heterogeneous diagnoses with multiple etiologies and symptoms. Whether epilepsy should be identified as a disease or disorder or as a symptom of a disease is often the subject of debate. Previously, the International League Against Epilepsy (ILAE) defined epilepsy as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition" following "at least one epileptic seizure."[9] More recently, the ILAE defined epilepsy as a "disease" rather than a "disorder" because "the term 'disorder' is poorly understood by the public and minimizes the serious nature of epilepsy."[10] The International Bureau for Epilepsy concurred with this redefinition.[10] In addition, the definition was changed to identify a person as having epilepsy after the occurrence of any of the following events[10]:

Epilepsy most often presents in childhood or in older adulthood.

- at least two unprovoked seizures more than 24 hours apart

- one unprovoked seizure with a high probability of recurrence over the next 10 years
- diagnosis of an electroclinical syndrome (formerly called an "epilepsy syndrome") upon evaluation

Although epilepsy is considered "resolved" in people with epilepsy who have taken no epilepsy medication for at least five years and have remained seizure-free for 10 years, there is no guarantee that seizures will not recur. In addition, the neurocognitive consequences of epilepsy, which vary widely, may persist even after seizure activity has resolved.[11, 12]

Table 1. Common Electroclinical Syndromes and Other Epilepsies[13]

Neonatal
• Benign familial neonatal epilepsy[a] • Early myoclonic encephalopathy[a]
Infancy
• West syndrome[a] • Myoclonic epilepsy in infancy[a] • Dravet syndrome[a]
Childhood
• Benign epilepsy with centrotemporal spikes[a] • Childhood absence epilepsy[a] • Lennox–Gastaut syndrome[a]
Adolescence
• Juvenile absence epilepsy[a] • Juvenile myoclonic epilepsy[a] • Epilepsy with generalized tonic–clonic seizures alone[a]
Without specific age relationship
• Familial focal epilepsy with variable foci • Reflex epilepsies (for example, photosensitive epilepsy or reading epilepsy)
Structural–metabolic
• Angioma • Degenerative conditions (for example, Alzheimer's disease or multiple sclerosis) • Hemimegalencephaly[a] • Heterotopias • Infection (for example, encephalitis or meningitis) • Neurocutaneous syndromes (for example, tuberous sclerosis or Sturge–Weber syndrome)[a] • Perinatal insults • Stroke • Trauma (closed or open head injuries) • Tumor (various brain tumors)

[a] Epilepsies that are considered electroclinical syndromes.

REVISED ETIOLOGIC CLASSIFICATIONS AND TERMINOLOGY

Epilepsy may be caused by a variety of factors, including perinatal anoxia, congenital malformations of the brain, genetic disorders, infectious disease, metabolic disorders, cerebrovascular disease, traumatic brain injury, neoplasms, toxins, and degenerative nerve diseases. Seizures can also be triggered by sleep deprivation, poor nutrition, dehydration, photic and other forms of stimulation, stress, and alcohol or drug use or withdrawal. Although about one-third of all epilepsies have no known cause,[13] a number of genetic discoveries and improved techniques in neuroimaging and neurophysiologic testing have greatly increased our understanding of the pathophysiology, diagnosis, and treatment of epilepsy and have contributed to an ongoing discussion within the ILAE regarding development of a new seizure classification system to replace the 1981 classification system and 1989 classification of the electroclinical syndromes of epilepsy. Previously the ILAE used the following categories to classify epilepsy etiology[14]:

- "primary," or "idiopathic," in which no underlying cause can be identified other than a possible hereditary tendency
- "secondary," or "symptomatic," in which symptoms are presumed to result from a known central nervous system (CNS) disorder
- cryptogenic, in which symptoms are presumed to be secondary, although no cause has been determined

The proposed update to the etiologic classification system uses, instead, the following concepts and terminology to describe epilepsy[13]:

- "genetic," in which seizures are the "core symptom" of the disease and the epilepsy is believed to result from known or presumed genetic defects
- "structural–metabolic," in which the patient not only has epilepsy but also has a structural or metabolic disorder that is associated with elevated risk of developing epilepsy under certain conditions
- "unknown cause," in which no cause has been identified, although it's understood that the epilepsy may result from an unrecognized genetic defect or other disorder

The revised terminology of the ILAE limits the use of the word "syndrome" to "a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder" that is often associated with a particular age of onset, seizure type, electroencephalogram (EEG) pattern, and "other features which, when taken together, permit a specific diagnosis" (see Table 1).[13] Epilepsy that is not associated with a distinctive electroclinical pattern is described in terms of factors such as known etiology, specific brain lesions, signs, and symptoms.

Table 2. Epileptic Seizure Classification[13, 16]

Focal seizures

- Simple focal
  - Consciousness is preserved
  - Signs can include motor, somatosensory, or special sensory; autonomic symptoms or signs; psychic symptoms (disturbances of higher cerebral function)
- Complex focal
  - Simple focal onset followed by impairment in consciousness
  - Impairment of consciousness at onset
- Focal seizures evolving into secondarily generalized seizures that are tonic–clonic, clonic, or tonic
  - Simple focal seizures evolving into generalized seizures
  - Complex focal seizures evolving into generalized seizures
  - Simple focal seizures evolving into complex focal seizures evolving into generalized seizures

Generalized seizures

- Absence
  - Absence seizures
    - Impairment in consciousness may include mild clonic, atonic, or tonic components; automatisms, autonomic components
  - Atypical absence seizures
    - Include changes in muscle tone that are more pronounced than in typical absence seizures, and onset or cessation that is not abrupt
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic–clonic seizures
- Atonic seizures

Status epilepticus

- Focal
  - Motoric (or "Jacksonian")
  - Very localized motoric: epilepsia partialis continua (a brain disorder that brings on brief [lasting seconds to minutes], recurrent focal motor seizures that are resistant to treatment)
- Generalized
  - Absence
  - Tonic–clonic

Unknown

- Neonatal seizures
- Infantile spasms

SIGNS AND SYMPTOMS

The most visible sign of epilepsy is an epileptic seizure—a transient event that is considered one element of the disease of epilepsy. A seizure results from abnormal discharges in the brain that abruptly and temporarily alter cerebral function. Most epileptic seizures last for less than two minutes, and arise from abnormal neuronal activity in the brain that is either excessive or synchronous.[9, 15] Some seizures are considered nonepileptic. These include seizures that are not associated with electrical changes on an EEG, such as those resulting from conversion disorder, syncope, sleep disorders, or movement disorders.

There are many types of classified and unclassified epileptic seizures (see Table 2).[13, 16] The clinical signs and symptoms that characterize a seizure are related to the brain area or areas affected (see Table 3). For a list of terms that describe the different seizures, see *Common Seizure Terms*.

Generalized seizures affect both hemispheres of the brain and are not associated with preictal (preseizure) symptoms. Consciousness may be impaired briefly, as with absence seizures (brief staring spells accompanied by a lapse of consciousness), or for longer periods, as with tonic–clonic (convulsive) seizures. Typically, generalized seizures are convulsive, though some (absence seizures and atonic seizures,

for example, in which the person loses muscle tone) are not.

Focal, or partial, seizures originate in one area of the brain. They may involve impaired consciousness (complex focal seizures) or not (simple focal seizures). Focal seizures are not convulsive unless they spread ("secondarily generalize") to the other side of the brain and transform into a tonic–clonic seizure. Because any seizure can secondarily generalize, it is important for family members of people with epilepsy to know seizure first aid and have a seizure treatment plan.

Focal seizures may be preceded by preictal symptoms, such as a feeling, subjective sensation, or physical symptom that "warns" of an impending seizure. In children, a preictal symptom can be as simple as a mood or behavioral change that a caregiver identifies as consistently preceding a seizure.

Both generalized and focal seizures may include changes in respiratory or autonomic systems, vocalizations, movement, cognition, sensations, or consciousness. Postictal (postseizure) symptoms may include confusion, fatigue, headache, transient focal weakness (Todd's paralysis), communication difficulties, muscle aches, memory changes, or other brain symptoms.

Status epilepticus. When a person has a prolonged generalized tonic–clonic seizure or at least two back-to-back seizures without full recovery (a return to baseline), the event is called convulsive status epilepticus (SE) and considered a medical emergency. Seizures that last five minutes or longer typically do not stop spontaneously.[17] In studies conducted on white populations in industrialized countries, the annual incidence of SE is 20 per 100,000, rising to 86 per 100,000 among adults ages 60 and older, although data on how incidence may be affected by race, ethnicity, and sex are limited.[18] Dham and colleagues examined demographic trends in the United States between 1979 and 2010, using data from the U.S. National Hospital Discharge Survey.[19] Their analysis of the 760,117 SE discharges showed that incidence of SE had increased from 3.5 to 12.5 per 100,000 during that period and that the sex distribution was nearly even (50.3% men versus 49.7% women). Men, however, had an earlier age of onset than women (mean age, 38.3 versus 43.6) and a slightly higher in-hospital mortality rate. Annual incidence of SE during the period studied was higher among blacks (13.7 per 100,000) and other nonwhites (7.4 per 100,000) than among whites (6.9 per 100,000), with black men having the highest cumulative annual incidence rate (15 per 100,000). Whites, however, had a higher in-hospital mortality rate (10%) than blacks (7.4%) and other nonwhites (9.3%), and black men had the lowest in-hospital mortality rate (6%). Convulsive SE can cause cerebral functional changes, neuronal injury, or death if medical treatment is not provided. Some epileptologists have suggested that any seizure lasting at least five minutes should be considered SE and treated accordingly.[17, 18]

All epileptic seizure types can evolve into prolonged SE episodes. Nonconvulsive SE may be more subtle in appearance. It includes both focal and absence seizures. Etiology, age, degree to which consciousness is impaired at presentation, severity of the underlying disease, and duration of SE have all been identified as important prognostic factors.[18, 20] An EEG can assist with the diagnosis and help clinicians determine the most appropriate medical interventions. With rapid treatment, it may be possible to prevent neuronal damage, systemic complications, and death from SE.

In children, SE is typically precipitated by such events as fever, infection, head trauma, or brain tumors. In adults, SE is commonly caused by acute or previous stroke or intracranial hemorrhage, metabolic abnormalities (such as hyponatremia), drug or alcohol toxicity, or such chronic processes as brain tumors or alcoholism.[17] In children and adults receiving epilepsy treatment, SE may also occur if serum levels of antiepileptic medication fall too low. The short-term mortality rate for SE is about 20% but may be as high as 40% in the presence of certain comorbidities.[18]

Table 3. Clinical Signs and Symptoms of Seizure Based on Location of Electrical Disturbance in the Brain

Frontal
• Motoric movements such as jerking of one or more limbs • Movements of head and eyes to one side or the other, which may be sudden or abrupt • Speech arrest or vocal sounds, such as moans, cries, or incomprehensible utterances
Temporal
• Emotions such as fear, sadness, pleasure • Vivid memory flashbacks • Humming or buzzing noises • Feelings of déjà vu • Smells or tastes that are intense or unpleasant
Parietal
• Sensations such as tingling in one area or side of the body
Occipital
• Flashing lights in part of the field of vision

THE PATHOPHYSIOLOGIC CASCADE

The differential diagnosis for epilepsy is comprehensive and includes a number of cardiovascular, neuromuscular, and psychiatric disorders (see *Differential Diagnosis for Epilepsy*). The brain is a network of interconnected neurons that can produce a wide array of synchronized activities, including those

Common Seizure Terms

Absence – brief stare of less than 30 seconds
Atonic – loss of tone
Clonic – jerking
Complex – consciousness altered
Focal (or partial) – originating in a single area of the brain
Generalized – affecting both hemispheres of the brain
Myoclonic – muscular jerking
Simple – consciousness preserved
Tonic – stiff

that trigger epileptic seizures. Both focal and tonic–clonic seizures have been associated with recurrent excitatory interactions between pyramidal cells in the cerebral cortex or hippocampus, whereas absence seizures result from the abnormal oscillatory activity of excitatory and inhibitory brain cells in the thalamus and cerebral cortex.[21]

Both experimental and clinical studies suggest that inflammation plays an important role in the pathophysiology of epilepsy.[22] According to the proposed pathophysiologic cascade, an injurious event—either within the peripheral lymphoid tissues, such as autoimmunity or infection, or in the CNS, such as trauma, stroke, or febrile seizures—may precipitate brain inflammation and trigger the development of epilepsy at any time during a person's life.[22] The inflammatory cascade of cytokines, danger signals, complement proteins, cyclooxygenase, chemokines, and cell adhesion molecules causes leukocytes (in the case of peripheral injury) or glial and neuronal cells (in the case of CNS injury) to disrupt the blood–brain barrier. This in turn alters the function of neurotransmitters and brain cells, creating an environment of increased excitability that allows epilepsy to occur.[22] Such insights into the pathophysiology of epileptic seizures have pointed to brain inflammation as a possible target for intervention.

EVALUATING EPILEPSY

A diagnosis of epilepsy is usually based on

- clinical description of the seizure.
- a thorough patient history.
- a complete physical assessment, including results of laboratory and diagnostic tests.

For an acute first seizure evaluated in the ED, laboratory tests should include a complete blood cell count and an electrolyte panel.[23] Other tests routinely performed when a patient presents to an ED for seizure evaluation include a toxicology screening. In febrile patients who are disoriented or display impaired consciousness, or in afebrile patients who are immunocompromised, lumbar puncture may be performed to rule out infections such as meningitis or encephalitis as the root cause of the seizure. In addition, an EEG should be ordered to assist in determining seizure type, possible epilepsy syndrome, and treatment management decisions. A normal EEG does not rule out epilepsy, nor does an abnormal EEG necessarily establish epilepsy, although seizure recurrence is more likely in patients with epileptiform abnormalities on an EEG.

A first seizure is often initially evaluated and treated by a primary care provider. If a person with epilepsy has an abnormal neurologic examination or focal epilepsy or fails to respond to the first antiepileptic medication prescribed, then a referral to a neurologist or epilepsy center for further evaluation is warranted.

Further evaluation of the epilepsy disorder may include neuropsychological, psychiatric, physical therapy, and occupational therapy assessment. In addition, video EEG monitoring may be used to determine type of epilepsy, investigate treatment failure, and evaluate patients for epilepsy surgery. Video EEG allows clinicians to compare clinical events and electrographic findings, though it may require hospitalization, depending on the duration of monitoring required and the importance of obtaining a sleep pattern. Following a focal seizure or an abnormal neurologic examination, magnetic resonance imaging (MRI) of the brain may be obtained to evaluate the brain for anatomic abnormalities. Other possible tests used to evaluate patients for epilepsy surgery include

- interictal (between-seizure) positron emission tomography, or single-photon emission computerized tomography performed at seizure onset, to evaluate brain function.
- magnetoencephalography, functional MRI, or both, to visualize brain activity.
- the intracarotid sodium amobarbital test (the Wada test) to determine cerebral dominance of language, speech, and memory.

Differential Diagnosis for Epilepsy

Cardiovascular disorders
Migraine
Movement disorders, including tics
Nonepileptic seizures
Psychiatric illness
Sleep disorders
Stroke or transient ischemic attack
Syncope
Transient global amnesia

The goal of epilepsy surgery evaluation is to determine the location of seizure onset and whether surgery on that area could alleviate symptoms without causing loss of function or ability.

EPILEPSY AS A SPECTRUM DISORDER

There is evidence that seizures, mental and behavioral health problems, and neurodevelopmental disorders often have similar underlying pathologies, suggesting that epilepsy is a spectrum disorder. An estimated 45% to 50% of people with epilepsy also have a cognitive or psychiatric diagnosis.[12, 24] In some studies, both psychiatric diagnoses and subtle cognitive impairment preceded the development of seizures.[25] Approximately 30% of adults with epilepsy have depression, anxiety, or both.[26] In a large population-based cohort study, cognitive dysfunction was diagnosed in 55%, 26%, and 9% of nearly 65,000 people with epilepsy who were ages five or younger, six to 18, and 19 to 34, respectively.[26] Although the prevalence of autism spectrum disorder was 1.3% in people with epilepsy in this study, 75% of those who had the condition were children and adolescents, representing a prevalence of 4.3% for people with epilepsy under age 18.[26] Similarly, the association between epilepsy and attention deficit–hyperactivity disorder (ADHD) was strong. The overall prevalence of ADHD among people with epilepsy was 3.4%, but in those ages 18 and younger it was 12.8%. Even children with epilepsy who have no severe cognitive deficits often have subtle but diffuse deficits in memory, attention, processing speed, and other domains.[27]

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Given the high prevalence of cognitive and psychological disorders among people with epilepsy, nurses are encouraged to follow evidence-based, consensus recommendations for the screening, assessment, treatment, and follow-up of behavioral health in people with epilepsy.[28-31] In addition to depression and anxiety screening, recent data support systematically evaluating patients for potential adverse effects of antiepileptic drugs; these effects can worsen in the presence of depression or anxiety disorders.[24]

Keep in mind that some antiepileptic drugs can affect mood and behavior and others interfere with the action of antidepressants. For example, valproic acid (Depakene and others), carbamazepine (Tegretol and others), oxcarbazepine (Trileptal, Oxtellar XR), and lamotrigine (Lamictal), which have mood-stabilizing properties, may positively affect mood, whereas levetiracetam (Keppra), topiramate (Topamax and others), or zonisamide (Zonegran) may cause or worsen depression, and patients taking a cytochrome P450 enzyme–inducing antiepileptic drug, such as carbamazepine, phenobarbital, or phenytoin (Dilantin, Phenytek), may never experience the optimal effect of a prescribed antidepressant.[32] In addition, any increase or decrease in antiepileptic drug dose must be monitored closely in patients who have a history of mood disorder to ensure that, as the medication is titrated or the patient weaned, any negative effects on mood and sleep dissipate.

Patients with mood or behavioral disorders should be encouraged to consider cognitive–behavioral techniques that teach problem solving and coping skills or target aspects of epilepsy self-management and antiepileptic drug adherence. In general, studies show that these skills-based interventions may be effective in improving psychological well-being, increasing knowledge of epilepsy, and enhancing adjustment.[33]

PSYCHOSOCIAL ISSUES

Because of the nature of epilepsy—the fact that it may limit mobility if driving is restricted, or include such symptoms as refractory seizures or loss of continence—people with epilepsy may experience a myriad of psychosocial challenges. Even in the 21st century, epilepsy remains a highly stigmatized condition. Misinformation about epilepsy continues to reinforce this stigma, weakening social support for affected patients. For example, a survey of 93 human resource professionals found that, out of 10 chronic conditions or disabilities—which included cancer in remission, depression, a history of heart problems, AIDS, mild intellectual disability, spinal cord injury, and epilepsy or seizures—subjects were least likely to hire people with known epilepsy or seizures.[34, 35] In addition to feeling stigmatized, people with epilepsy report having less self-efficacy for managing seizures and poor health-related quality of life,[35] although health care utilization is known to be greater in this group than among the general population.[8, 36] Longitudinal studies show that adults who were diagnosed with childhood epilepsy are less likely to be well educated.[37] According to the American Epilepsy Society, people with epilepsy are two to three times as likely to be unemployed as the general population.[38] The difficulty experienced by adults with epilepsy in finding and sustaining employment contributes to their social isolation. To make informed decisions about reproduction, women with epilepsy must consider the impact of epilepsy and its treatments on maternal health. Epilepsy may impede a person's independence and success in a variety of domains. Health care providers must advocate for their patients, assist them in identifying and linking to community resources, and promote "living well with epilepsy" by expanding the public's

core knowledge about epilepsy and encouraging positive attitudes and behavior toward people with epilepsy.[8] ▼

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