The Epilepsies and Seizures

Hope Through Research

National Institute of Neurological Disorders
and Stroke
National Institutes of Health

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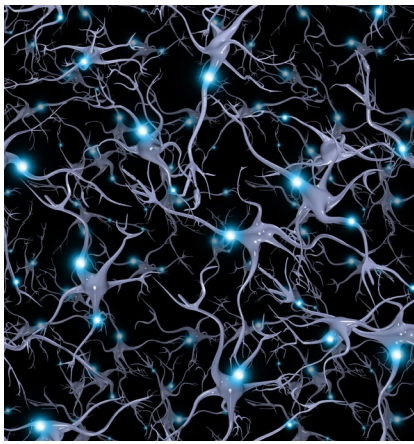
What are the epilepsies?



Clusters of brain cells (neurons) sometimes fire or signal faster than normal—as many as 500 times a second. This surge of excessive electrical activity causes seizures.

The epilepsies are chronic neurological disorders in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally and cause seizures. Neurons normally generate electrical and chemical signals that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. During a seizure, many neurons fire (signal) at the same time – as many as 500 times a second, much faster than normal. This surge of excessive electrical activity happening at the same time causes involuntary movements, sensations, emotions, and behaviors and the temporary disturbance of normal neuronal activity may cause a loss of awareness.

Epilepsy can be considered a spectrum disorder because of its different causes, different seizure types, its ability to vary in severity and impact from person to person, and its range of co-existing conditions. Some people may have *convulsions*[1] (sudden onset of repetitive general contraction of muscles) and lose consciousness. Others may simply stop what they are doing, have a brief lapse of awareness, and stare into space for a short period. Some people have seizures very infrequently, while

[1] Terms in italics appear in a Glossary found at the end of this document.

other people may experience hundreds of seizures each day. There also are many different types of epilepsy, resulting from a variety of causes. Recent adoption of the term "the epilepsies" underscores the diversity of types and causes.

In general, a person is not considered to have epilepsy until he or she has had two or more unprovoked seizures separated by at least 24 hours. In contrast, a provoked seizure is one caused by a known precipitating factor such as a high fever, nervous system infections, acute traumatic brain injury, or fluctuations in blood sugar or electrolyte levels.

Anyone can develop epilepsy. About 2.3 million adults and more than 450,000 children and adolescents in the United States currently live with epilepsy. Each year, an estimated 150,000 people are diagnosed with epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds, and ages. In the United States alone, the annual costs associated with the epilepsies are estimated to be $15.5 billion in direct medical expenses and lost or reduced earnings and productivity.

The majority of those diagnosed with epilepsy have seizures that can be controlled with drug therapies and surgery. However, as much as 30 to 40 percent of people with epilepsy continue to have seizures because available treatments do not completely control their seizures (called intractable or medication resistant epilepsy).

While many forms of epilepsy require lifelong treatment to control the seizures, for some people the seizures eventually go away. The odds of becoming seizure-free are not as good for adults or for children with severe epilepsy syndromes, but it is possible that seizures may decrease or even stop over time. This is more likely if the epilepsy starts in childhood, has been well-controlled by medication, or if the person has had surgery to remove the brain focus of the abnormal cell firing.

About 2.3 million adults and more than 450,000 children and adolescents in the U.S. live with epilepsy.

Many people with epilepsy lead productive lives, but some will be severely impacted by their epilepsy. Medical and research advances in the past two decades have led to a better understanding of the epilepsies and seizures. More than 20 different medications and a variety of dietary treatments and surgical techniques (including two devices) are now available and may provide good control of seizures. Devices can modulate brain activity to decrease seizure frequency. Advance neuroimaging can identify brain abnormalities that give rise to seizures which can be cured by neurosurgery. Even dietary changes can effectively treat certain types of epilepsy. Research on the underlying causes of the epilepsies, including identification of genes for some forms of epilepsy, has led to a greatly improved understanding of these disorders that may lead to more effective treatments or even to new ways of preventing epilepsy in the future.

What causes the epilepsies?

The epilepsies have many possible causes, but for up to half of people with epilepsy a cause is not known. In other cases, the epilepsies are clearly linked to genetic factors, developmental brain abnormalities, infection, traumatic brain injury, stroke, brain tumors, or other identifiable problems. Anything that disturbs the normal pattern of neuronal activity – from illness to brain damage to abnormal brain development – can lead to seizures.

The epilepsies may develop because of an abnormality in brain wiring, an imbalance of nerve signaling in the brain (in which some cells either over-excite or over-inhibit other brain cells from sending messages), or some combination of these factors. In some pediatric conditions abnormal brain wiring causes other problems such as intellectual impairment.

In other persons, the brain's attempts to repair itself after a head injury, stroke, or other problem may inadvertently generate abnormal nerve connections that lead to epilepsy. Brain malformations and abnormalities in brain wiring that occur during brain development also may disturb neuronal activity and lead to epilepsy.

Genetics

Genetic mutations may play a key role in the development of certain epilepsies. Many types of epilepsy affect multiple blood-related family members, pointing to a strong inherited genetic component. In other cases, gene mutations may

occur spontaneously and contribute to development of epilepsy in people with no family history of the disorder (called "*de novo*" mutations). Overall, researchers estimate that hundreds of genes could play a role in the disorders.

Several types of epilepsy have been linked to mutations in genes that provide instructions for ion channels, the "gates" that control the flow of ions in and out of cells to help regulate neuronal signaling. For example, most infants with *Dravet syndrome*, a type of epilepsy associated with seizures that begin before the age of one year, carry a mutation in the SCN1A gene that causes seizures by affecting sodium ion channels.

Genetic mutations also have been linked to disorders known as the *progressive myoclonic epilepsies*, which are characterized by ultra-quick muscle contractions (myoclonus) and seizures over time. For example, *Lafora disease*, a severe, progressive form of myoclonic epilepsy that begins in childhood, has been linked to a gene that helps to break down carbohydrates in brain cells.

Mutations in genes that control neuronal migration – a critical step in brain development – can lead to

Researchers estimate that hundreds of genes may play a role in the epilepsies.

areas of misplaced or abnormally formed neurons, called cortical dysplasia, in the brain that can cause these mis-wired neurons to misfire and lead to epilepsy.

Other genetic mutations may not cause epilepsy, but may influence the disorder in other ways. For example, one study showed that many people with certain forms of epilepsy have an abnormally active version of a gene that results in resistance to anti-seizure drugs. Genes also may control a person's susceptibility to seizures, or *seizure threshold*, by affecting brain development.

Other Disorders

Epilepsies may develop as a result of brain damage associated with many types of conditions that disrupt normal brain activity. Seizures may stop once these conditions are treated and resolved. However, the chances of becoming seizure-free after the primary disorder is treated are uncertain and vary depending on the type of disorder, the brain region that is affected, and how much brain damage occurred prior to treatment. Examples of conditions that can lead to epilepsy include:

- Brain tumors, including those associated with neurofibromatosis or tuberous sclerosis complex, two inherited conditions that cause benign tumors called hamartomas to grow in the brain
- Head trauma
- Alcoholism or alcohol withdrawal
- Alzheimer's disease
- Strokes, heart attacks, and other conditions that

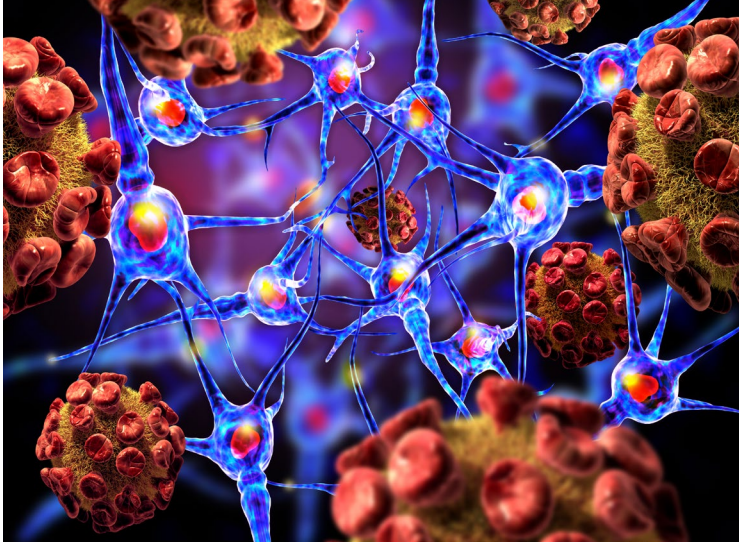
deprive the brain of oxygen (a significant portion of new-onset epilepsy in elderly people is due to stroke or other cerebrovascular disease)

- Abnormal blood vessel formation (arteriovenous malformations) or bleeding in the brain (hemorrhage)
- Inflammation of the brain
- Infections such as meningitis, HIV, and viral encephalitis

Cerebral palsy or other developmental neurological abnormalities may also be associated with epilepsy. About 20 percent of seizures in children can be attributed to developmental neurological conditions. Epilepsies often co-occur in people with abnormalities of brain development or other neurodevelopmental disorders. Seizures are more common, for example, among individuals with autism spectrum disorder or intellectual impairment. In one study, fully a third of children with autism spectrum disorder had treatment-resistant epilepsy.

Seizure Triggers

Seizure triggers do not cause epilepsy but can provoke first seizures in those who are susceptible or can cause seizures in people with epilepsy who otherwise experience good seizure control with their medication. Seizure triggers include alcohol consumption or alcohol withdrawal, dehydration or missing meals, stress, and hormonal changes associated with the menstrual cycle. In surveys of people with epilepsy, stress is the most commonly reported seizure trigger. Exposure to toxins



Many conditions—including infections such as meningitis and viral encephalitis—that disrupt normal brain activity can lead to epilepsy. This illustration depicts a virus attacking brain cells.

or poisons such as lead or carbon monoxide, street drugs, or even excessively large doses of antidepressants or other prescribed medications also can trigger seizures.

Sleep deprivation is a powerful trigger of seizures. Sleep disorders are common among people with the epilepsies and appropriate treatment of co-existing sleep disorders can often lead to improved control of seizures. Certain types of seizures tend to occur during sleep, while others are more common during times of wakefulness, suggesting to physicians how to best adjust a person's medication.

For some people, visual stimulation can trigger seizures in a condition known as photosensitive epilepsy. Stimulation can include such things as flashing lights or moving patterns.

What are the different kinds of seizures?

Seizures are divided into two major categories – *focal seizures* and *generalized seizures*. However, there are many different types of seizures in each of these categories. In fact, doctors have described more than 30 different types of seizures.

Focal Seizures

Focal seizures originate in just one part of the brain. About 60 percent of people with epilepsy have focal seizures. These seizures are frequently described by the area of the brain in which they originate. Many people are diagnosed with focal frontal lobe or medial temporal lobe seizures.

In some focal seizures, the person remains conscious but may experience motor, sensory, or psychic feelings (for example, intense *dejà vu* or memories) or sensations that can take many forms. The person may experience sudden and unexplainable feelings of joy, anger, sadness, or nausea. He or she also may hear, smell, taste, see, or feel things that are not real and may have movements of just one part of the body, for example, just one hand.

In other focal seizures, the person has a change in consciousness, which can produce a dreamlike experience. The person may display strange, repetitious behaviors such as blinks, twitches, mouth movements (often like chewing or swallowing, or even walking in a circle). These repetitious movements are called *automatisms*. More complicated actions, which may seem purposeful, can also occur involuntarily. Individuals may also

continue activities they started before the seizure began, such as washing dishes in a repetitive, unproductive fashion. These seizures usually last just a minute or two.

Some people with focal seizures may experience *auras* – unusual sensations that warn of an impending seizure. Auras are usually focal seizures without interruption of awareness (e.g., *dejà vu*, or an unusual abdominal sensation) but some people experience a true warning before an actual seizure. An individual's symptoms, and the progression of those symptoms, tend to be similar every time. Other people with epilepsy report experiencing a *prodrome*, a feeling that a seizure is imminent lasting hours or days.

The symptoms of focal seizures can easily be confused with other disorders. The strange behavior and sensations caused by focal seizures also can be mistaken for symptoms of narcolepsy, fainting, or even mental illness. Several tests and careful monitoring may be needed to make the distinction between epilepsy and these other disorders.

Generalized Seizures

Generalized seizures are a result of abnormal neuronal activity that rapidly emerges on both sides of the brain. These seizures may cause loss of consciousness, falls, or a muscle's massive contractions. The many kinds of generalized seizures include:

- *Absence seizure*s may cause the person to appear to be staring into space with or without slight twitching of the muscles.

- *Tonic seizures* cause stiffening of muscles of the body, generally those in the back, legs, and arms.
- *Clonic seizures* cause repeated jerking movements of muscles on both sides of the body.
- *Myoclonic seizures* cause jerks or twitches of the upper body, arms, or legs.
- *Atonic seizures* cause a loss of normal muscle tone, which often leads the affected person to fall down or drop the head involuntarily.
- *Tonic-clonic seizures* cause a combination of symptoms, including stiffening of the body and repeated jerks of the arms and/or legs as well as loss of consciousness.
- Secondary generalized seizures.

Not all seizures can be easily defined as either focal or generalized. Some people have seizures that begin as focal seizures but then spread to the entire brain. Other people may have both types of seizures but with no clear pattern.

Some people recover immediately after a seizure, while others may take minutes to hours to feel as they did before the seizure. During this time, they may feel tired, sleepy, weak, or confused. Following focal seizures or

Absence seizures—a type of generalized seizure—can cause a person to appear to be staring into space.

seizures that started from a focus, there may be local symptoms related to the function of that focus. Certain characteristics of the post-seizure (or *post-ictal*) state may help locate the region of the brain where the seizure occurred. A classic example is called Todd's paralysis, a temporary weakness in the part of the body that was affected depending on where in the brain the focal seizure occurred. If the focus is in the temporal lobe, post-ictal symptoms may include language or behavioral disturbances, even psychosis. After a seizure, some people may experience headache or pain in muscles that contracted.

What are the different kinds of epilepsy?

Just as there are many different kinds of seizures, there are many different kinds of epilepsy. Hundreds of different *epilepsy syndromes* – disorders characterized by a specific set of symptoms that include epilepsy as a prominent symptom – have been identified. Some of these syndromes appear to be either hereditary or caused by *de novo* mutations. For other syndromes, the cause is unknown. Epilepsy syndromes are frequently described by their symptoms or by where in the brain they originate.

Absence epilepsy is characterized by repeated seizures that cause momentary lapses of consciousness. These seizures almost always begin in childhood or adolescence and tend to run in families, suggesting that they may be at least partially due to genetic factors. Individuals may show purposeless movements during their seizures,

such as a jerking arm or rapidly blinking eyes, while others may have no noticeable symptoms except for brief times when they appear to be staring off into space. Immediately after a seizure, the person can resume whatever he or she was doing. However, these seizures may occur so frequently (in some cases up to 100 or more a day) that the person cannot concentrate in school or other situations. Childhood absence epilepsy usually stops when the child reaches puberty. Although most children with childhood absence epilepsy have a good prognosis, there may be long-lasting negative consequences and some children will continue to have absence seizures into adulthood and/or go on to develop other seizure types.

Epilepsy syndromes are frequently described by their symptoms or by where they originate in the brain.

Frontal lobe epilepsy is a common epilepsy syndrome that features brief focal seizures that may occur in clusters. It can affect the part of the brain that controls movement and involves seizures that can cause muscle weakness or abnormal, uncontrolled movement such as twisting, waving the arms or legs, eye deviation to one side, or grimacing, and are usually associates with some loss of awareness. Seizures usually occur when the person is asleep but also may occur while awake.

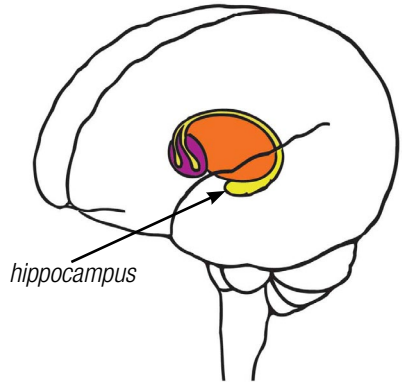
Temporal lobe epilepsy, or TLE, is the most common epilepsy syndrome with focal seizures. These seizures are often associated with auras of nausea, emotions (such as *déjà vu* or fear), or unusual smell or taste. The seizure itself is a brief period of impaired consciousness which may appear as a staring spell,

dream-like state, or repeated automatisms. TLE often begins in childhood or teenage years. Research has shown that repeated temporal lobe seizures are often associated with shrinkage and scarring (sclerosis) of the hippocampus. The hippocampus is important for memory and learning. It is not clear whether localized asymptomatic seizure activity over years causes the hippocampal sclerosis.

Neocortical epilepsy is characterized by seizures that originate from the brain's cortex, or outer layer. The seizures can be either focal or generalized. Symptoms may include unusual sensations, visual hallucinations, emotional changes, muscle contractions, convulsions, and a variety of other symptoms, depending on where in the brain the seizures originate.

There are many other types of epilepsy that begin in infancy or childhood. For example, *infantile spasms* are clusters of seizures that usually begin before the age of 6 months. During these seizures the infant may drop their head, jerk an arm, bend at the waist and/or cry out. Children with *Lennox-Gastaut syndrome* have several different types of seizures, including atonic seizures, which cause sudden falls and are also called *drop attacks*. Seizure onset is usually before age four years. This severe form of epilepsy can be very difficult to treat effectively. *Rasmussen's encephalitis* is a progressive form of epilepsy in which half the brain shows chronic inflammation. Some childhood epilepsy syndromes, such as childhood absence epilepsy, tend to go into remission or stop entirely during adolescence, whereas other syndromes such as *juvenile myoclonic epilepsy*

(which features jerk-like motions upon waking) and Lennox-Gastaut syndrome are usually present for life once they develop. Children with Dravet syndrome have seizures that start before age one and later in infancy develop into other seizure types.



According to research, repeated temporal lobe seizures are often associated with shrinkage and scarring of the hippocampus—a part of the brain important for memory and learning.

Hypothalamic hamartoma is a rare form of epilepsy that first occurs during childhood and is associated with malformations of the hypothalamus at the base of the brain. People with hypothalamic hamartoma have seizures that resemble laughing or crying. Such seizures frequently go unrecognized and are difficult to diagnose.

When are seizures not epilepsy?

While any seizure is cause for concern, having a seizure does not by itself mean a person has epilepsy. First seizures, febrile seizures, nonepileptic events, and eclampsia (a life-threatening condition that can occur in pregnant women) are examples of conditions involving seizures that may not be associated with epilepsy. Regardless of the type of seizure, it's important to inform your doctor when one occurs.

First Seizures

Many people have a single seizure at some point in their lives, and it can be provoked or unprovoked, meaning that they can occur with or without any obvious triggering factor. Unless the person has suffered brain damage or there is a family history of epilepsy or other neurological abnormalities, the majority of single seizures usually are not followed by additional seizures. Medical disorders which can provoke a seizure include low blood sugar, very high blood sugar in diabetics, disturbances in salt levels in the blood (sodium, calcium, magnesium), eclampsia during or after pregnancy, impaired function of the kidneys, or impaired function of the liver. Sleep deprivation, missing meals, or stress may serve as seizure triggers in susceptible people.

Many people with a first seizure will never have a second seizure, and physicians often counsel against starting antiseizure drugs at this point. In some cases where additional epilepsy risk factors are present, drug treatment after the first seizure may help prevent future seizures. Evidence suggests that it may be beneficial to begin antiseizure medication once a person has had a second unprovoked seizure, as the chance of future seizures increases significantly after this occurs. A person with a pre-existing brain problem, for example, a prior stroke or traumatic brain injury, will have a higher risk of experiencing a second seizure. In general, the decision to start antiseizure medication is based on the doctor's assessment of many factors that influence how likely it is that another seizure will occur in that person.

In one study that followed individuals for an average of 8 years, 33 percent of people had a second seizure within 4 years after an initial seizure. People who did not have a second seizure within that time remained seizure-free for the rest of the study. For people who did have a second seizure, the risk of a third seizure was about 73 percent by the end of 4 years. Among those with a third unprovoked seizure, the risk of a fourth was 76 percent.

Febrile Seizures

Not infrequently a child will have a seizure during the course of an illness with a high fever. These seizures are called *febrile seizures*. Antiseizure medications following a febrile seizure are generally not warranted unless certain other conditions are present: a family history of epilepsy, signs of nervous system impairment prior to the seizure, or a relatively prolonged or complicated seizure. The risk of subsequent non-febrile seizures is low unless one of these factors is present.

Results from a study funded by the National Institute of Neurological Disorders and Stroke (NINDS) suggested that certain findings using diagnostic imaging of the hippocampus may help identify which children with prolonged febrile seizures are subsequently at increased risk of developing epilepsy.

Febrile seizures, which occur in infants and children, may arise during the course of an illness with a high fever.

Researchers also have identified several different genes that influence the risks associated with febrile seizures in certain families. Studying these genes may lead to new understandings of how febrile seizures occur and perhaps point to ways of preventing them.

Nonepileptic Events

An estimated 5 to 20 percent of people diagnosed with epilepsy actually have non-epileptic seizures (NES), which outwardly resemble epileptic seizures, but are not associated with seizure-like electrical discharge in the brain. Non-epileptic events may be referred to as psychogenic non-epileptic seizures or PNES, which do not respond to antiseizure drugs. Instead, PNES are often treated by cognitive behavioral therapy to decrease stress and improve self-awareness.

A history of traumatic events is among the known risk factors for PNES. People with PNES should be evaluated for underlying psychiatric illness and treated appropriately. Two studies together showed a reduction in seizures and fewer coexisting symptoms following treatment with cognitive behavioral therapy. Some people with epilepsy have psychogenic seizures in addition to their epileptic seizures.

Other nonepileptic events may be caused by narcolepsy (sudden attacks of sleep), Tourette syndrome (repetitive involuntary movements called tics), cardiac arrhythmia (irregular heart beat), and other medical conditions with symptoms that resemble seizures. Because symptoms of these disorders can look very much like epileptic seizures, they are often mistaken for epilepsy.

Are there special risks associated with the epilepsies?

Although most people with epilepsy lead full, active lives, there is an increased risk of death or serious disability associated with epilepsy. There may be an increased risk of suicidal thoughts or actions related to some antiseizure medications that are also used to treat mania and bipolar disorder. Two life-threatening conditions associated with the epilepsies are *status epilepticus and sudden unexpected death in epilepsy (SUDEP)*.

Status Epilepticus

Status epilepticus is a potentially life-threatening condition in which a person either has an abnormally prolonged seizure or does not fully regain consciousness between recurring seizures. Status epilepticus can be convulsive (in which outward signs of a seizure are observed) or nonconvulsive (which has no outward signs and is diagnosed by an abnormal EEG). Nonconvulsive status epilepticus may appear as a sustained episode of confusion, agitation, loss of consciousness, or even coma.

Any seizure lasting longer than 5 minutes should be treated as though it was status epilepticus. There is some evidence that 5 minutes is sufficient to damage neurons and that seizures are unlikely to end on their own, making it necessary to seek medical care immediately. One study showed that 80 percent of people in status epilepticus who received medication within 30 minutes of seizure onset eventually stopped having seizures, whereas only 40 percent

recovered if 2 hours had passed before they received medication. The mortality rate can be as high as 20 percent if treatment is not initiated immediately.

Researchers are trying to shorten the time it takes for antiseizure medications to be administered. A key challenge has been establishing an intravenous (IV) line to deliver injectable antiseizure drugs in a person having convulsions. An NINDS-funded study on status epilepticus found that when paramedics delivered the medication midazolam to the muscles using an autoinjector, similar to the EpiPen drug delivery system used to treat serious allergic reactions, seizures could be stopped significantly earlier compared to when paramedics took the time to give lorazepam intravenously. In addition, drug delivery by autoinjector was associated with a lower rate of hospitalization compared with IV delivery (see the NINDS news story, *http://www.ninds.nih.gov/news_and_events/news_articles/RAMPART_results.htm*).

Results from the RAMPART study showed that drug delivery using an autoinjector (similar to the EpiPen) is faster and may be a more effective way to stop status epilepticus.

Sudden Unexpected Death in Epilepsy (SUDEP)

For reasons that are poorly understood, people with epilepsy have an increased risk of dying suddenly for no discernible reason. Some studies suggest

that each year approximately one case of SUDEP occurs for every 1,000 people with the epilepsies. For some, this risk can be higher, depending on several factors. People with more difficult to control seizures tend to have a higher incidence of SUDEP.

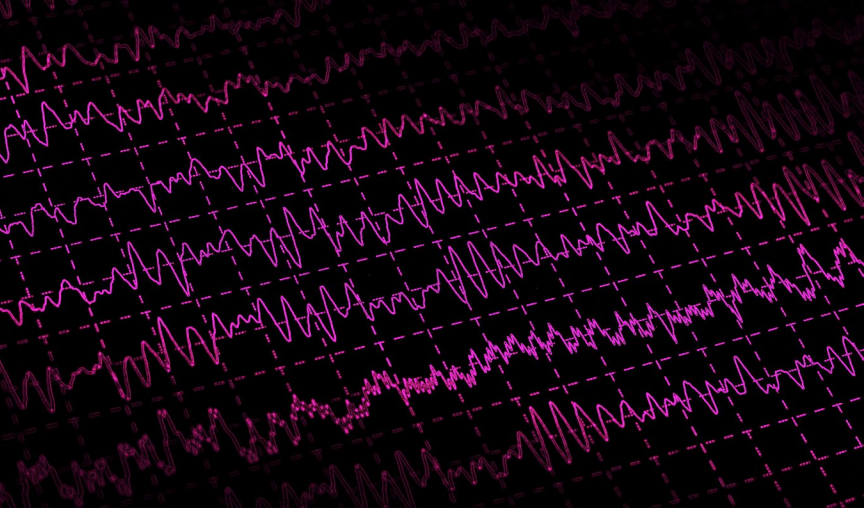
SUDEP can occur at any age. Researchers are still unsure why SUDEP occurs, although some research points to abnormal heart and respiratory function due to gene abnormalities (ones which cause epilepsy and also affect heart function). People with epilepsy may be able to reduce the risk of SUDEP by carefully taking all antiseizure medication as prescribed. Not taking the prescribed dosage of medication on a regular basis may increase the risk of SUDEP in individuals with epilepsy, especially those who are taking more than one medication for their epilepsy.

How are the epilepsies diagnosed?

A number of tests are used to determine whether a person has a form of epilepsy and, if so, what kind of seizures the person has.

Imaging and Monitoring

An electroencephalogram, or EEG, can assess whether there are any detectable abnormalities in the person's brain waves and may help to determine if antiseizure drugs would be of benefit. This most common diagnostic test for epilepsy records electrical activity detected by electrodes placed on the scalp. Some people who are diagnosed with a specific syndrome may have abnormalities in brain



Doctors use EEG to detect abnormalities in a person's brain waves and to determine if antiseizure drugs will be beneficial.

activity, even when they are not experiencing a seizure. However, some people continue to show normal electrical activity patterns even after they have experienced a seizure. These occur if the abnormal activity is generated deep in the brain where the EEG is unable to detect it. Many people who do not have epilepsy also show some unusual brain activity on an EEG. Whenever possible, an EEG should be performed within 24 hours of an individual's first seizure. Ideally, EEGs should be performed while the person is drowsy as well as when he or she is awake because brain activity during sleep and drowsiness is often more revealing of activity resembling epilepsy. Video monitoring may be used in conjunction with EEG to determine the nature of a person's seizures and to rule out other disorders such as psychogenic non-epileptic seizures, cardiac arrhythmia, or narcolepsy that may look like epilepsy.

A magnetoencephalogram (MEG) detects the magnetic signals generated by neurons to help detect surface abnormalities in brain activity. MEG can

be used in planning a surgical strategy to remove focal areas involved in seizures while minimizing interference with brain function.

The most commonly used brain scans include CT (computed tomography), PET (positron emission tomography) and MRI (magnetic resonance imaging). CT and MRI scans reveal structural abnormalities of the brain such as tumors and cysts, which may cause seizures. A type of MRI called functional MRI (fMRI) can be used to localize normal brain activity and detect abnormalities in functioning. SPECT (single photon emission computed tomography) is sometimes used to locate seizure foci in the brain. A modification of SPECT, called ictal SPECT, can be very helpful in localizing the brain area generating seizures. In a person admitted to the hospital for epilepsy monitoring, the SPECT blood flow tracer is injected within 30 seconds of a seizure, then the images of brain blood flow at the time of the seizure are compared with blood flow images taken in between seizures. The seizure onset area shows a high blood flow region on the scan. PET scans can be used to identify brain regions with lower than normal metabolism, a feature of the epileptic focus after the seizure has stopped.

Medical History

Taking a detailed medical history, including symptoms and duration of the seizures, is still one of the best methods available to determine what kind of seizures a person has had and to determine any form of epilepsy. The medical history should include details about any past illnesses or other

Blood samples may be used to screen for disorders associated with seizures and to check for underlying health conditions.

symptoms a person may have had, as well as any family history of seizures. Since people who have suffered a seizure often do not remember what happened, caregiver or other accounts of seizures are vital to this evaluation. The person who experienced the seizure is asked about any warning experiences. The observers will be asked to provide a detailed description of events in the timeline they occurred.

Blood Tests

Blood samples may be taken to screen for metabolic or genetic disorders that may be associated with the seizures. They also may be used to check for underlying health conditions such as infections, lead poisoning, anemia, and diabetes that may be causing or triggering the seizures. In the emergency department it is standard procedure to screen for exposure to recreational drugs in anyone with a first seizure.

Developmental, Neurological, and Behavioral Tests

Tests devised to measure motor abilities, behavior, and intellectual ability are often used as a way to determine how epilepsy is affecting an individual. These tests also can provide clues about what kind of epilepsy the person has.

Can the epilepsies be prevented?

At this time there are no medications or other therapies that have been shown to prevent epilepsy. In some cases, the risk factors that lead to epilepsy can be modified. Good prenatal care, including treatment of high blood pressure and infections during pregnancy, may prevent brain injury in the developing fetus that may lead to epilepsy and other neurological problems later. Treating cardiovascular disease, high blood pressure, and other disorders that can affect the brain during adulthood and aging also may prevent some cases of epilepsy. Prevention or early treatment of infections such as meningitis in high-risk populations may also prevent cases of epilepsy. Also, the wearing of seatbelts and bicycle helmets, and correctly securing children in car seats, may avert some cases of epilepsy associated with head trauma.

How can epilepsy be treated?

Accurate diagnosis of the type of epilepsy a person has is crucial for finding an effective treatment. There are many different ways to successfully control seizures. Doctors who treat the epilepsies come from many different fields of medicine and include neurologists, pediatricians, pediatric neurologists, internists, and family physicians, as well as neurosurgeons. An epileptologist is someone who has completed advanced training and specializes in treating the epilepsies.

Once epilepsy is diagnosed, it is important to begin treatment as soon as possible. Research suggests that medication and other treatments may be less successful once seizures and their consequences become established. There are several treatment approaches that can be used depending on the individual and the type of epilepsy. If seizures are not controlled quickly, referral to an epileptologist at a specialized epilepsy center should be considered, so that careful consideration of treatment options, including dietary approaches, medication, devices, and surgery, can be performed in order to gain optimal seizure treatment.

Medications

The most common approach to treating the epilepsies is to prescribe antiseizure drugs. More than 20 different antiseizure medications are available today, all with different benefits and side effects. Most seizures can be controlled with one drug (called *monotherapy*). Deciding on which drug to prescribe, and at what dosage, depends on many different factors, including seizure type, lifestyle and age, seizure frequency, drug side effects, medicines for other conditions, and, for a woman, whether she is pregnant or will become pregnant. It may take several months to determine the best drug and dosage. If one treatment is unsuccessful, another may work better.

For many people with epilepsy, seizures can be controlled with monotherapy at the optimal dosage. Combining medications may amplify side effects such as fatigue and dizziness, so

doctors usually prescribe just one drug whenever possible. Combinations of drugs, however, are still sometimes necessary for some forms of epilepsy that do not respond to monotherapy.

Seizure Medications

Generic	Brand Name (United States)
Carbamazepine	Carbatrol, Tegretol
Clobazam	Frisium, Onfi
Clonazepam	Klonopin
Diazepam	Diastat, Diazepam, Valium
Divalproex Sodium	Depakote, Depakote ER
Eslicarbazepine Acetate	Aptiom
Ezogabine	Potiga
Felbamate	Felbatol
Gabapentin	Neurontin
Lacosimide	Vimpat
Lamotrigine	Lamictal
Levetiracetam	Keppra, Keppra XR
Lorazepam	Ativan
Oxcarbazepine	Oxtellar, Oxtellar XR, Trileptal
Perampanel	Fycompa
Phenobarbital	
Phenytoin	Dilantin, Phenytek,
Pregabalin	Lyrica
Primidone	Mysoline
Rufinamide	Banzel
Tiagabine Hydrochloride	Gabitril
Topiramate	Topamax, Topamax XR
Valproic Acid	Depakene
Vigabatrin	Sabril

When starting any new antiseizure medication, a low dosage will usually be prescribed initially followed by incrementally higher dosages, sometimes with blood-level monitoring, to determine when the optimal dosage has been reached. It may take time for the dosage to achieve optimal seizure control while minimizing side effects. The latter are usually worse when first starting a new medicine.

Most side effects of antiseizure drugs are relatively minor, such as fatigue, dizziness, or weight gain. Antiseizure medications have differing effects on mood: some may worsen depression, where others may improve depression or stabilize mood. However, severe and life-threatening reactions such as allergic reactions or damage to the liver or bone marrow can occur. Antiseizure medications can interact with many other drugs in potentially harmful ways. Some antiseizure drugs can cause the liver to speed the metabolism of other drugs and make the other drugs less effective, as may be the case with oral contraceptives. Since people can become more sensitive to medications as they age, blood levels of medication may need to be checked occasionally to see if dosage adjustments are necessary. The effectiveness of a medication can diminish over time, which can increase the risk of seizures. Some citrus fruit and products, in particular grapefruit juice, may interfere with the breakdown of many drugs, including antiseizure medications – causing them to build up in the body, which can worsen side effects.

Some people with epilepsy may be advised to discontinue their antiseizure drugs after 2-3 years have passed without a seizure. Others may

Antiseizure medications are the most common treatment for epilepsy. There are more than 20 different such medications available today—all with different benefits and side effects.

be advised to wait for 4 to 5 years. Discontinuing medication should always be done with supervision of a health care professional. It is very important to continue taking antiseizure medication for as long as it is prescribed. Discontinuing medication too early is one of the major reasons people who have been seizure-free start having new seizures and can lead to status epilepticus. Some evidence also suggests that uncontrolled seizures may trigger changes in the brain that will make it more difficult to treat the seizures in the future.

The chance that a person will eventually be able to discontinue medication varies depending on the person's age and his or her type of epilepsy. More than half of children who go into remission with medication can eventually stop their medication without having new seizures. One study showed that 68 percent of adults who had been seizure-free for 2 years before stopping medication were able to do so without having more seizures and 75 percent could successfully discontinue medication if they had been seizure-free for 3 years. However, the odds of successfully stopping medication are not as good for people with a family history of epilepsy, those who need multiple medications, those with focal seizures, and those who continue to have abnormal EEG results while on medication.

There are specific syndromes in which certain antiseizure medications should not be used because they may make the seizures worse. For example, carbamazepine can worsen epilepsy in children diagnosed with Dravet syndrome.

Diet

Dietary approaches and other treatments may be more appropriate depending on the age of the individual and the type of epilepsy. A high-fat, very low carbohydrate ketogenic diet is often used to treat medication-resistant epilepsies. The diet induces a state known as ketosis, which means that the body shifts to breaking down fats instead of carbohydrates to survive. A ketogenic diet effectively reduces seizures for some people, especially children with certain forms of epilepsy. Studies have shown that more than 50 percent of people who try the ketogenic diet have a greater than 50 percent improvement in seizure control and 10 percent experience seizure freedom. Some children are able to discontinue the ketogenic diet after several years and remain seizure-free, but this is done with strict supervision and monitoring by a physician.

The ketogenic diet is not easy to maintain, as it requires strict adherence to a limited range of foods. Possible side effects include impaired growth due to nutritional deficiency and a buildup of uric acid in the blood, which can lead to kidney stones.

Researchers are looking at modified versions of and alternatives to the ketogenic diet. For example, studies show promising results for a modified Atkins diet and for a low-glycemic-index treatment, both of

which are less restrictive and easier to follow than the ketogenic diet, but well-controlled randomized controlled trials have yet to assess these approaches.

Surgery

Evaluation of persons for surgery is generally recommended only after focal seizures persist despite the person having tried at least two appropriately chosen and well-tolerated medications, or if there is an identifiable brain *lesion* (a dysfunctional part of the brain) believed to cause the seizures. When someone is considered to be a good candidate for surgery experts generally agree that it should be performed as early as possible.

Surgical evaluation takes into account the seizure type, the brain region involved, and the importance of the area of the brain where seizures originate (called the focus) for everyday behavior. Prior to surgery, individuals with epilepsy are monitored intensively in order to pinpoint the exact location in the brain where seizures begin. Implanted electrodes may be used to record activity from the surface of the brain, which yields more detailed information than an external scalp EEG. Surgeons usually avoid operating in areas of the brain that are necessary for speech, movement, sensation, memory and thinking, or other important abilities. fMRI can be used

Surgery can significantly reduce or even halt seizures in some people, although it involves some level of risk.

to locate such "eloquent" brain areas involved in an individual.

While surgery can significantly reduce or even halt seizures for many people, any kind of surgery involves some level of risk. Surgery for epilepsy does not always successfully reduce seizures and it can result in cognitive or personality changes as well as physical disability, even in people who are excellent candidates for it. Nonetheless, when medications fail, several studies have shown that surgery is much more likely to make someone seizure-free compared to attempts to use other medications. Anyone thinking about surgery for epilepsy should be assessed at an epilepsy center experienced in surgical techniques and should discuss with the epilepsy specialists the balance between the risks of surgery and desire to become seizure-free.

Even when surgery completely ends a person's seizures, it is important to continue taking antiseizure medication for some time. Doctors generally recommend continuing medication for at least two years after a successful operation to avoid recurrence of seizures.

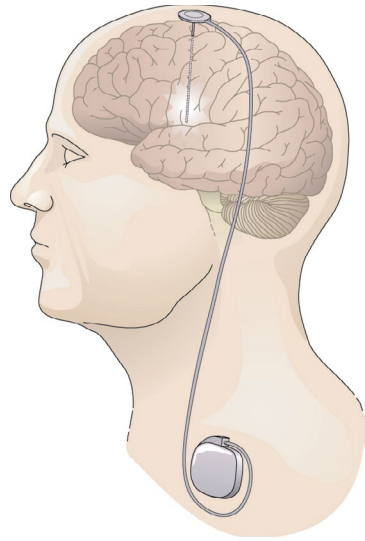
Surgical procedures for treating epilepsy disorders include:

- Surgery to remove a seizure focus involves removing the defined area of the brain where seizures originate. It is the most common type of surgery for epilepsy, which doctors may refer to as a *lobectomy* or *lesionectomy*, and is appropriate only for focal seizures that originate in just one area of the brain. In general, people have a better chance of becoming seizure-free

after surgery if they have a small, well-defined seizure focus. The most common type of lobectomy is a *temporal lobe resection*, which is performed for people with medial temporal lobe epilepsy. In such individuals one hippocampus (there are two, one on each side of the brain) is seen to be shrunken and scarred on an MRI scan.

- *Multiple subpial transection* may be performed when seizures originate in part of the brain that cannot be removed. It involves making a series of cuts that are designed to prevent seizures from spreading into other parts of the brain while leaving the person's normal abilities intact.
- *Corpus callosotomy*, or severing the network of neural connections between the right and left halves (*hemispheres*) of the brain, is done primarily in children with severe seizures that start in one half of the brain and spread to the other side. Corpus callosotomy can end drop attacks and other generalized seizures. However, the procedure does not stop seizures in the side of the brain where they originate, and these focal seizures may even worsen after surgery.
- *Hemispherectomy* and *hemispherotomy* involve removing half of the brain's cortex, or outer layer. These procedures are used predominantly in children who have seizures that do not respond to medication because of damage that involves only half the brain, as occurs with conditions such as Rasmussen's encephalitis. While this type of surgery is very excessive and is performed only when other therapies have failed, with intense rehabilitation, children can recover many abilities.

Devices



Deep brain stimulation, which uses mild electrical impulses to stimulate the brain, has been tried as a treatment for epilepsy in several different brain areas.

Electrical stimulation of the brain remains a therapeutic strategy of interest for people with medication-resistant forms of epilepsy who are not candidates for surgery.

The vagus nerve stimulation device for the treatment of epilepsy was approved by the U.S. Food and Drug Administration (FDA) in 1997. The *vagus nerve stimulator* is surgically implanted under the skin of the chest and is attached to the vagus nerve in the lower neck. The device delivers short bursts of electrical energy to the brain via the vagus nerve. On average, this stimulation reduces seizures by about 20 - 40 percent. Individuals usually cannot stop taking epilepsy medication because of the stimulator, but they often experience fewer seizures and they may be able to reduce the dosage of their medication.

Responsive stimulation involves the use of an implanted device that analyzes brain activity patterns to detect a forthcoming seizure. Once detected, the device administers an intervention, such as electrical stimulation or a fast-acting drug to prevent the seizure from occurring. These devices also are known as closed-loop systems. NeuroPace, one of the first responsive stimulation, closed-loop devices, received premarket approval by the FDA in late 2013 and is available for adults with refractory

epilepsy (hard to treat epilepsy that does not respond well to trials of at least two medicines).

Experimental devices: not approved by the FDA for use in the United States (as of March 2015)

- Deep brain stimulation using mild electrical impulses has been tried as a treatment for epilepsy in several different brain regions. It involves surgically implanting an electrode connected to an implanted pulse generator – similar to a heart pacemaker – to deliver electrical stimulation to specific areas in the brain to regulate electrical signals in neural circuits. Stimulation of an area called the *anterior thalamic nucleus* has been particularly helpful in providing at least partial relief from seizures in people who had medication-resistant forms of the disorder.
- A report on *trigeminal nerve stimulation* (using electrical signals to stimulate parts of the trigeminal nerve and affected brain regions) showed efficacy rates similar to those for vagal nerve stimulation, with responder rates hovering around 50 percent. (A responder is defined as someone having greater than a 50 percent reduction in seizure frequency.) Freedom from seizures, although reported, remains rare for both methods. At the time of this writing, a trigeminal nerve stimulation device was available for use in Europe, but it had not yet been approved in the United States.
- Transcutaneous magnetic stimulation involves a device being placed outside the head to produce a magnetic field to induce an electrical current in nearby areas of the brain. It has been shown to reduce cortical activity associated with specific epilepsy syndromes.

What is the impact of the epilepsies on daily life?

The majority of people with epilepsy can do the same things as people without the disorder and have successful and productive lives. In most cases it does not affect job choice or performance. One-third or more of people with epilepsy, however, may have cognitive or neuropsychiatric co-concurring symptoms that can negatively impact their quality of life. Many people with epilepsy are significantly helped by available therapies, and some may go months or years without having a seizure. However, people with treatment-resistant epilepsy can have as many as hundreds of seizures a day or they can have one seizure a year with sometimes disabling consequences. On average, having treatment-resistant epilepsy is associated with an increased risk of cognitive impairment, particularly if the seizures developed in early childhood. These impairments may be related to the underlying conditions associated with the epilepsy rather than to the epilepsy itself.

Mental Health and Stigmatization

Depression is common among people with epilepsy. It is estimated that one of every three persons with epilepsy will have depression in the course of his or her lifetime, often with accompanying symptoms of anxiety disorder. In adults, depression and anxiety are the two most frequent mental health-related diagnoses. In adults, a depression screening questionnaire specifically designed for epilepsy helps health care professions identify people who need

treatment. Depression or anxiety in people with epilepsy can be treated with counseling or most of the same medications used in people who don't have epilepsy. People with epilepsy should not simply accept that depression is part of having epilepsy and should discuss symptoms and feelings with health care professionals.

Children with epilepsy have a higher risk of developing depression and/or attention deficit hyperactivity disorder than their peers.

Children with epilepsy also have a higher risk of developing depression and/or attention deficit hyperactivity disorder compared with their peers. Behavioral problems may precede the onset of seizures in some children.

Children are especially vulnerable to the emotional problems caused by ignorance or the lack of knowledge among others about epilepsy. This often results in stigmatization, bullying, or teasing of a child who has epilepsy. Such experiences can lead to behaviors of avoidance in school and other social settings. Counseling services and support groups can help families cope with epilepsy in a positive manner.

Driving and Recreation

Most states and the District of Columbia will not issue a driver's license to someone with epilepsy unless the person can document that she/he has been seizure-free for a specific amount of time

(the waiting period varies from a few months to several years). Some states make exceptions for this policy when seizures don't impair consciousness, occur only during sleep, or have long auras or other warning signs that allow the person to avoid driving when a seizure is likely to occur. Studies show that the risk of having a seizure-related accident decreases as the length of time since the last seizure increases. Commercial drivers' licenses have additional restrictions. In addition, people with epilepsy should take extra care if a job involves operation of machinery or vehicles.

The risk of seizures also limits people's recreational choices. Individuals may need to take precautions with activities such as climbing, sailing, swimming, or working on ladders. Studies have not shown any increase in seizures due to sports, although these studies have not focused on any activity in particular. There is some evidence that regular exercise may improve seizure control in some people, but this should be done under a doctor's supervision. The benefits of sports participation may outweigh the risks and coaches or other leaders can take appropriate safety precautions. Steps should be taken to avoid dehydration, overexertion, and hypoglycemia, as these problems can increase the risk of seizures.

Education and Employment

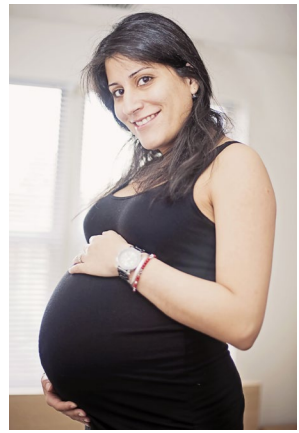
By law, people with epilepsy (or disabilities) in the United States cannot be denied employment or access to any educational, recreational, or other activity because of their epilepsy. However, significant barriers still exist for people with epilepsy in school and

work. Antiseizure drugs may cause side effects that interfere with concentration and memory. Children with epilepsy may need extra time to complete schoolwork, and they sometimes may need to have instructions or other information repeated for them. Teachers should be told what to do if a child in their classroom has a seizure, and parents should work with the school system to find reasonable ways to accommodate any special needs their child may have.

Pregnancy and motherhood

Women with epilepsy are often concerned about whether they can become pregnant and have a healthy child. Epilepsy itself does not interfere with the ability to become pregnant. With the right planning, supplemental vitamin use, and medication adjustments prior to pregnancy, the odds of a woman with epilepsy having a healthy pregnancy and a healthy child are similar to a woman without a chronic medical condition.

Children of parents with epilepsy have about 5 percent risk of developing the condition at some point during life, in comparison to about a 1 percent risk in a child in the general population. However, the risk of developing epilepsy increases if a parent has a clearly hereditary form of the disorder. Parents who are worried that their epilepsy may be hereditary may wish to consult a genetic counselor to determine their risk of passing on the disorder.



It is important for pregnant women with epilepsy to work with a team of health care providers to learn about any special risks associated with the medicines they may be taking.

Other potential risks to the developing child of a woman with epilepsy or on antiseizure medication include increased risk for major congenital malformations (also known as birth defects) and adverse effects on the developing brain. The types of birth defects that have been most commonly reported with antiseizure medications include cleft lip or cleft palate, heart problems, abnormal spinal cord development (spina bifida), urogenital defects, and limb-skeletal defects.

Discussion about seizure medications should occur early between the health care professional and any woman with epilepsy who is in her childbearing years.

Some antiseizure medications, particularly valproate, are known to increase the risk of having a child with birth defects and/or neurodevelopmental problems, including learning disabilities, general intellectual disabilities, and autism spectrum disorder. It is important that a woman work with a team of providers that includes her neurologist and her obstetrician to learn about any special risks associated with her epilepsy and the medications she may be taking.

Although planned pregnancies are essential to ensuring a healthy pregnancy, effective birth control is also essential. Some antiseizure medications that induce the liver's metabolic capacity can interfere with the effectiveness of hormonal contraceptives (e.g., birth control pills, vaginal ring). Women who are on these enzyme-inducing antiseizure medications and using hormonal contraceptives may need to switch to a different kind of birth control that is more effective (such as different intrauterine devices, progestin implants, or long-lasting injections).

Prior to a planned pregnancy, a woman with epilepsy should meet with her health care team to reassess the current need for antiseizure medications and to determine a) the optimal medication to balance seizure control and avoid birth defects and b) the lowest dose for going into a planned pregnancy. Any transitions to either a new medication or dosage should be phased in prior to the pregnancy, if possible. If a woman's seizures are controlled for the 9 months prior to pregnancy, she is more likely to continue to have seizure control during pregnancy. For all women with epilepsy during pregnancy, approximately 15-25 percent will have seizure worsening, but another 15-25 percent will have seizure improvement. As a woman's body changes during pregnancy, the dose of seizure medication may heed to be increased. For most medicines, monthly monitoring of blood levels of the antiseizure medicines can help to assure continued seizure control. Many of the birth defects seen with antiseizure medications occur in the first six weeks of pregnancy, often before a woman is aware she is pregnant. In addition, up to 50 percent of pregnancies in the U.S. are unplanned. For these reasons, the discussion about the medications should occur early between the health care professional and any woman with epilepsy who is in her childbearing years.

For all women thinking of becoming pregnant, using supplemental folic acid beginning prior to conception and continuing the supplement during pregnancy is an important way to lower the risk for birth defects and developmental delays. Prenatal multivitamins should also be used prior to the

beginning of pregnancy. Pregnant women with epilepsy should get plenty of sleep and avoid other triggers or missed medications to avoid worsening of seizures.

Most pregnant women with epilepsy can deliver with the same choices as women without any medical complications. During the labor and delivery, it is important that the woman be allowed to take her same formulations and doses of antiseizure drugs at her usual times; it is often helpful for her to bring her medications from home. If a seizure does occur during labor and delivery, intravenous short-acting medications can be given if necessary. It is unusual for the newborns of women with epilepsy to experience symptoms of withdrawal from the mother's antiseizure medication (unless she is on phenobarbital or a standing dose of benzodiazepines), but the symptoms resolve quickly and there are usually no serious or long-term effects.

The use of antiseizure medications is considered safe for women who choose to breastfeed their child. On very rare occasions, the baby may become excessively drowsy or feed poorly, and these problems should be closely monitored. However, experts believe the benefits of breastfeeding outweigh the risks except in rare circumstances. One large study showed that the children who were breastfed by mothers with epilepsy on antiseizure medications performed better on learning and developmental scales than the babies who were not breastfed. It is common for the antiseizure medication dosing to be adjusted again in the postpartum setting, especially if the dose was altered during pregnancy.

With the appropriate selection of safe antiseizure medicines during pregnancy, use of supplemental folic acid, and ideally, with pre-pregnancy planning, most women with epilepsy can have a healthy pregnancy with good outcomes for themselves and their developing child.

What research is being done on the epilepsies by the NINDS?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use the knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health (NIH), the leading supporter of biomedical research in the world. The NINDS conducts and supports research to better understand and diagnose epilepsy, develop new treatments, and ultimately, prevent epilepsy. Researchers hope to learn the epileptogenesis of these disorders – how the epilepsies develop, and how, where, and why neurons begin to display the abnormal firing patterns that cause epileptic seizures.

Mechanisms

Researchers are learning more about the fundamental processes – known as mechanisms – that lead to epileptogenesis. With every mechanism that is discovered come new potential targets for drug therapies to interrupt the processes that lead to the development of epilepsy. Basic science studies

NINDS conducts and supports research on epilepsy to better understand, diagnose, treat, and ultimately, prevent the disorder. Researchers hope to learn how the epilepsies develop, and how, where, and why brain cells display the abnormal firing patterns that cause seizures.

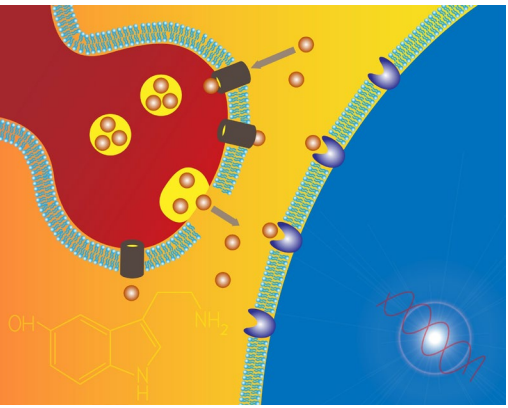
continue to investigate how neurotransmitters (chemicals which carry signals from one nerve cell to another) interact with brain cells to control nerve firing and how non-neuronal cells in the brain contribute to seizures. For example, studies are focusing on the role of gamma-aminobutyric acid (GABA), a key neurotransmitter that inhibits activity in the central nervous system. Research on GABA has led to drugs that alter the amount of this neurotransmitter in the brain or change how the brain responds to it. Researchers also are studying the role of excitatory neurotransmitters such as glutamate. In some cases, the epilepsies may result from changes in the ability of supportive brain cells called glia to regulate glutamate levels. Researchers have found that when astrocytes – a type of glial cell that play a critical housekeeping role by removing excessive levels of glutamate – are impaired, levels of

glutamate rise excessively in the spaces between brain cells, which may contribute to the onset of seizures.

The blood-brain barrier plays in important protective role between the circulatory systems and the fluid surrounding the brain, as it keeps toxins in the blood from reaching the brain. However, this protective layer of cells and other components can also block potentially beneficial medications from reaching the brain. Scientists are looking for ways to overcome this barrier for the sake of expanding therapeutic options. For example, in one study people with drug-resistant epilepsy are receiving infusions of neurotransmitter-specific agents directly into the epileptic focus.

In another study, researchers are looking at a protein that is part of the blood-brain barrier, called P-glycoprotein (P-gp). Levels of P-gp are higher in people with epilepsy than in people without it. These different levels of P-gp may explain why some people have seizures that do not respond well to medications. NINDS-funded researchers want to see if manipulating P-gp levels can affect the response to epilepsy medications.

The brain chemical serotonin helps neurons communicate. Previous research suggests that serotonin activity may be lower in brain areas where seizures start, and that increasing activity at the serotonin receptor site on nerve cells may help prevent seizures. NINDS-funded researchers are studying an experimental medication aimed at increasing the activity of serotonin receptors to see if it can reduce seizure frequency in people whose seizures are not well controlled on antiseizure medication.



Serotonin is a brain chemical that helps neurons communicate. Research suggests that serotonin activity may be lower in brain areas where seizures start, and that increasing serotonin activity may help prevent seizures.

Research has shown that the cell membrane that surrounds each neuron plays an important role in epilepsy because it allows neurons to generate electrical impulses. Scientists are studying details of the membrane structure, how molecules move in and out of membranes, and how the cell nourishes and repairs the membrane. A disruption in any of these processes may lead to seizures.

Ongoing research is focused on developing better animal models that more closely reflect the mechanisms that cause epilepsy in humans so that they can be used to more effectively screen potential treatments for the epilepsies.

Improving treatments

The NINDS Anticonvulsant Screening Program (ASP) (*www.ninds.nih.gov/research/asp*) provides a free compound screening service to identify candidate drugs to treat the epilepsies. The ASP annually has screened hundreds of new chemical agents from academic, industrial, and government participants using a battery of models of potential efficacy and side-effect liability. Results are compared to those obtained with standard marketed antiepileptic drugs. The ASP has played a role in

the identification and development of numerous marketed antiseizure drugs, including felbamate, topiramate, lacosamide, and retigabine. Current efforts emphasize unmet medical needs in epilepsy, such as treatments for refractory epilepsies, the development of epilepsy in previously unaffected individuals, and disease progression.

NINDS-funded researchers are looking at drug combinations that would help boost the effectiveness of medication therapy. For example, one trial is looking at the ability of an antianxiety medication to increase brain activity in specific regions, which could in turn decrease epileptic seizures.

Neonatal seizures frequently lead to epilepsy as well as to significant cognitive and motor disabilities. At the same time, safe and completely effective antiseizure medications for these newborns are lacking. Current treatment options are generally ineffective and have significant side effects. NINDS-funded investigators are working to identify better treatment options for neonates and to test them in randomized controlled trials.

Researchers continue to engineer technologic advances to assist in the diagnosis of the epilepsies and to identify the source (focus) of the seizures in the brain. For example, electrode arrays that are flexible enough to mold to the brain's complex surface provide unprecedented access for recording and stimulating brain activity, and possibly provide a way to deliver treatment. While these arrays have not yet been used in humans, they are a promising advance toward expanded options for epilepsy diagnosis and treatment.

Researchers are striving to make surgery for epilepsy safer by minimizing the language deficits that can occur afterwards. Using functional magnetic resonance imaging (fMRI) as well as other imaging technologies, researchers are helping to improve preoperative planning by more accurately mapping areas of the brain that are important for the ability to understand and speak language – which will help surgeons to preserve those areas during surgery. Doctors also are experimenting with brain scans called functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS) that can detect abnormalities in the brain's biochemical processes, and with near-infrared spectroscopy, a technique that can detect oxygen levels in brain tissue.

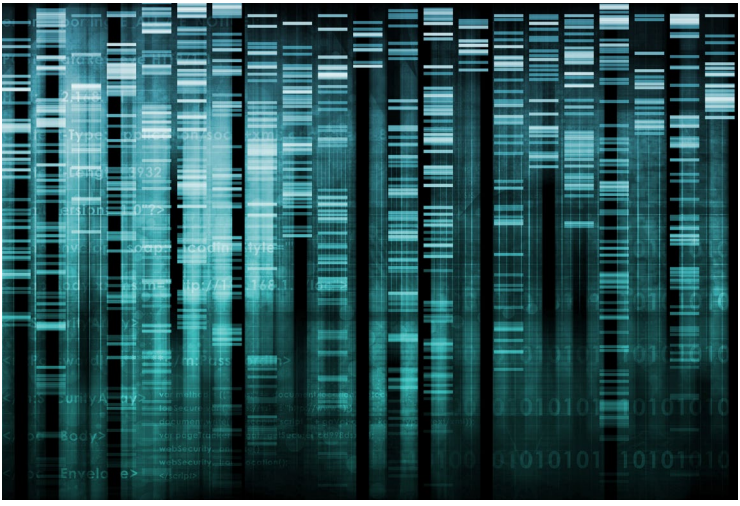
Researchers also continue to develop minimally-invasive approaches to treat an epilepsy focus via heat (thermoablation), transcranial ultrasound, or high-powered x-rays (stereotactic radiosurgery). For example, minimally invasive MRI-guided laser surgery is being studied for the treatment of the epilepsies associated with tumors such as hypothalamic hamartomas and tuberous sclerosis complex. The technique involves drilling a very small hole in the skull through which a thermal laser is inserted to ablate an epileptogenic zone under MRI-guidance.

Genetics

Advances in understanding the human genome have spurred continued efforts to identify genes responsible for epileptic conditions. NINDS

is a large supporter of research investigating genes responsible for epilepsies and disorders of human cognition that gain a foothold during early brain development. Continued progress in the identification of genetic causes of the epilepsies could guide the care and medical management of individuals and, in the case of heritable mutations, will help affected families understand their risks.

NINDS established its Epilepsy Centers without Walls Program in 2010 to address challenges and gaps in epilepsy research. The innovative program encourages collaborations, including sharing of data and resources, between researchers from a variety of disciplines and institutions regardless of geographic location, that may lead to advances in prevention, diagnosis, or treatment of the epilepsies and related comorbidities.



Learning more about the human genome has increased efforts to identify genes responsible for epilepsy. Continued progress to identify genetic causes of the epilepsies could help affected families understand their risks.

Epi4K is an NINDS-funded Epilepsy Center without Walls aimed at determining the genetic basis of various epilepsies. Epi4K investigators are analyzing the genomes of at least 4,000 people with well-characterized epilepsies. Through this work, researchers have successfully identified mutations associated with Dravet syndrome, infantile spasms, and Lennox-Gastaut syndrome. Most important, these discoveries will give researchers the basis for screening agents for their potential therapeutic effects.

The discovery of genetic mutations that are linked to specific epilepsy syndromes suggests the possibility of using gene-directed therapies to counter the effects of these mutations. Gene therapies remain the subject of many studies in animal models of epilepsy, and the number of potential approaches continues to expand. A common approach in gene therapy research uses viruses modified to be harmless to introduce new genes into brain cells, which then act as "factories" to produce potentially therapeutic proteins.

Cell therapy differs from gene therapy in that instead of introducing genetic material, cell therapy involves the transplantation of whole cells into a brain. In animal studies, for example, NINDS-funded researchers have successfully controlled seizures in mice by grafting special types of neurons that produce the inhibitory neurotransmitter GABA into the hippocampus region of their brains.

SUDEP (sudden unexpected death in epilepsy)

NINDS, non-profit lay and professional organizations, and the Centers for Disease Control and Prevention are providing significant funding toward studies aimed at better understanding SUDEP risk factors and mechanisms, which may point the way toward developing strategies for screening and prevention.

Early studies have described certain EEG patterns that may help identify people at elevated risk for SUDEP. Several devices in the early stages of development aim to provide a warning when a seizure has the potential to put someone at risk for SUDEP.

A second NINDS-funded Epilepsy Center without Walls project – the Center for SUDEP Research – is now underway and includes some of the world's foremost experts on SUDEP. The group will investigate potential causes of SUDEP, elucidate signs or symptoms that might make one more susceptible to SUDEP, and identify biological processes that may be targets for preventing SUDEP.

How can I help research on the epilepsies?

There are many ways that people with epilepsies and their families can help advance research.

- Pregnant women who are taking antiseizure drugs can help researchers learn how these drugs affect unborn children by participating in the Antiepileptic Drug Pregnancy Registry,

which is maintained by the Genetics and Teratology Unit of Massachusetts General Hospital. Women who enroll in the registry are given educational materials on pre-conception planning and perinatal care and are asked to provide information about the health of their children. (This information is kept confidential.) Information about the registry is available at *http://www2.massgeneral.org/aed/* or by calling 1-888-233-2334. Information also is available from sites of the NIH-sponsored study, Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD): *https://clinicaltrials.gov/ct2/show/NCT01730170*.

- Participating in a clinical study is an excellent opportunity to help researchers find better ways to safely detect, treat, or prevent epilepsy and therefore offer hope to people now and in the future. NINDS conducts clinical studies on the epilepsies at the NIH research campus in Bethesda, Maryland, and support epilepsy studies at medical research centers throughout the United States. But studies can be completed only if people volunteer to participate. By participating in a clinical study, health individuals and people living with epilepsy can

Clinical studies help researchers find better ways to detect, treat, or prevent disorders such as epilepsy. Participation in a clinical study is an excellent opportunity to offer hope to people with neurological disorders now and in the future.

greatly benefit the lives of those affected by this disorder. Interested individuals should talk with their health care professional about clinical studies and help to make the difference in improving the quality of life for all persons with epilepsy. For information about participating in a clinical study at the NIH and contact information for each study, see *http://patientinfo.ninds.nih.gov* and search for epilepsy. For information about additional NINDS-funded clinical studies on epilepsy and ways to participate, see *http://www.clinicaltrials.gov* and search for "epilepsy AND NINDS".

- People with epilepsy can help further research by making arrangements to donate tissue either at the time of surgery for epilepsy, or at the time of death. Researchers use the tissue to study epilepsy and other disorders so they can better understand what causes seizures. Below are some brain banks that accept tissue from individuals with epilepsy. Each brain bank may have different protocols for registering a potential donor. Individuals are strongly encouraged to contact a brain bank directly to preplan and learn what needs to be done ahead of the time of tissue donation.

The NIH NeuroBioBank (*https://neurobiobank.nih.gov/*) is an effort by the National Institutes of Health to coordinate the network of brain banks it supports in the United States. The brain tissue and data is collected, evaluated, stored, and made available to researchers via a network of brain and

tissue repositories in standardized way for the study of neurological, psychiatric and developmental disorders, including epilepsy. For a listing of participating NIH NeuroBioBank repositories and additional brain banks, see *https://neurobiobank.nih.gov/pages/researcher_resources/*.

What to do if you see someone having a seizure

- Roll the person on his or her side to prevent choking on any fluids or vomit.
- Cushion the person's head.
- Loosen any tight clothing around the neck.
- Don't restrict the person from moving or wandering unless he or she is in danger.
- Do NOT put anything into the person's mouth, not even medicine or liquid. These can cause choking or damage to the person's jaw, tongue, or teeth. Remember, people cannot swallow their tongues during a seizure or any other time.
- Remove any dangerous objects the person might hit or walk into during the seizure.
- Note how long the seizure lasts and what symptoms occurred so you can tell a doctor or emergency personnel if necessary.
- Stay with the person until the seizure ends.

Call 911 if:

- The person is pregnant or has diabetes.
- The seizure happened in water.
- The seizure lasts longer than 5 minutes.
- The person does not begin breathing normally or does not regain consciousness after the seizure stops.
- Another seizure starts before the person regains consciousness.
- The person injures himself or herself during the seizure.
- This is a first seizure or you think it might be. If in doubt, check to see if the person has a medical identification card or jewelry stating that they have epilepsy or a seizure disorder.

After the seizure ends, the person will probably be groggy and tired. He or she also may have a headache and be confused or embarrassed. Try to help the person find a place to rest. If necessary, offer to call a taxi, a friend, or a relative to help the person get home safely.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
301-496-5751
800-352-9424
www.ninds.nih.gov

In addition to NINDS, several other NIH institutes and centers also support research relevant to understanding, treating, or preventing seizures and epilepsy. More information on epilepsy and seizures research supported by the NINDS and other NIH components is available through the NIH RePORTER (*http://projectreporter.nih.gov*), a searchable database of current and previously funded research, as well as research results and publications.

Information also is available from the following organizations:

Citizens United for Research in Epilepsy (CURE)
430 W. Erie, Suite 210
Chicago, IL 60654
312-255-1801
800-765-7118
www.CUREepilepsy.org

The Charlie Foundation for Ketogenic Therapies
515 Ocean Avenue, Suite 602N
Santa Monica, CA 90402
310-393-2347
www.charliefoundation.org

Epilepsy Foundation
8301 Professional Place East, Suite 200
Landover, MD 20785-2353
301-459-3700
800-EFA-1000 (332-1000)
www.epilepsy.com

Hope for HH (Hope for Hypothalamic Hamartoma)
P. O. Box 721
Waddell, AZ 85355
http://hopeforhh.org

Intractable Childhood Epilepsy Alliance
PO Box 365
6360 Shallowford Road
Lewisville, NC 27023
336-946-1570
www.ice-epilepsy.org

LGS Foundation (Lennox-Gastaut Syndrome)
192 Lexington Avenue, Suite 212
New York, NY 10016
718-374-3800
www.lgsfoundation.org

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
203-744-0100
Voice Mail 800-999-NORD (6673)
www.rarediseases.org

RE Children's Project (Rasmussen's Encephalitis)
79 Christie Hill Road
Darien, CT 06820
917-971-2977
www.rechildrens.org

Dravet Syndrome Foundation
P.O. Box 16536
West Haven, CT 06516
203-392-1950
www.dravetfoundation.org

Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910
301-562-9890
800-225-6872
www.tsalliance.org

U.S. National Library of Medicine
National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983
888-346-3656
www.nlm.nih.gov

Glossary

Note: Due to the large number of epilepsy syndromes and treatments, only a few are discussed in this booklet. Additional information may be available from health care professionals, medical libraries, patient advocacy organizations, or by calling the NINDS Office of Communications and Public Liaison.

absence epilepsy — epilepsy in which the person has repeated absence seizures.

absence seizures — seizures seen in absence epilepsy, in which the person experiences a momentary loss in consciousness. The person may stare into space for several seconds and may have some twitching or mild jerking of muscles. An older term for absence seizures is petit mal seizures.

atonic seizures — seizures which cause a sudden loss of muscle tone, also called drop attacks.

auras — unusual sensations or movements that warn of an impending, more severe seizure. These auras are actually simple focal seizures in which the person maintains consciousness.

automatisms — automatic involuntary or mechanical actions.

clonic seizures — seizures that cause repeated jerking movements of muscles on both sides of the body.

***convulsions* —** sudden severe contractions of the muscles that may be caused by seizures.

***corpus callosotomy* —** surgery that severs the corpus callosum, or network of neural connections between the right and left hemispheres

***déjà vu* —** a sense that something has happened before.

***de novo* —** new, for the first time.

***Dravet syndrome* —** a type of intractable epilepsy that begins in infancy.

***drop attacks* —** seizures that cause sudden falls; another term for atonic seizures.

***epilepsy syndromes* —** disorders with a specific set of symptoms that include epilepsy.

***febrile seizures* —** seizures in infants and children that are associated with a high fever.

***focal seizures* —** seizures that occur in just one part of the brain.

***frontal lobe epilepsy* —** a type of epilepsy that originates in the frontal lobe of the brain. It usually involves a cluster of short seizures with a sudden onset and termination.

***generalized seizures* —** seizures that result from abnormal neuronal activity in many parts of the brain. These seizures may cause loss of consciousness, falls, or abnormal movements such as convulsions.

grand mal seizures **—** an older term for tonic-clonic seizures.

hemispheres **—** the right and left halves of the brain.

hemispherectomy **—** surgery involving the removal or disabling of one hemisphere of the brain.

hemispherotomy **—** removing half of the brain's outer layer (cortex).

hypothalamic hamartoma **—** a rare form of childhood epilepsy that is associated with malformations of the hypothalamus at the base of the brain.

infantile spasms **—** clusters of seizures that usually begin before the age of 6 months. During these seizures the infant may bend and cry out.

intractable **—** hard to treat; about 30 to 40 percent of people with epilepsy will continue to experience seizures even with the best available treatment.

juvenile myoclonic epilepsy **—** a type of epilepsy characterized by sudden muscle (myoclonic) jerks that usually begins in childhood or adolescence.

ketogenic diet **—** a strict diet rich in fats and low in carbohydrates that causes the body to break down fats instead of carbohydrates to survive.

Lafora disease **—** a severe, progressive form of epilepsy that begins in childhood and has been linked to a gene that helps to break down carbohydrates.

Lennox-Gastaut syndrome **—** a type of epilepsy that begins in childhood and usually causes several different kinds of seizures, including absence seizures.

lesion **—** damaged or dysfunctional part of the brain or other parts of the body.

lesionectomy **—** surgical removal of a specific brain lesion.

lobectomy **—** surgical removal of a lobe of the brain.

monotherapy **—** treatment with only one antiepileptic drug.

multiple subpial transection **—** a type of operation in which surgeons make a series of cuts in the brain that are designed to prevent seizures from spreading into other parts of the brain while leaving the person's normal abilities intact.

myoclonic seizures **—** seizures that cause sudden jerks or twitches, especially in the upper body, arms, or legs.

neocortical epilepsy **—** epilepsy that originates in the brain's cortex, or outer layer. Seizures can be either focal or generalized, and may cause strange sensations, hallucinations, or emotional changes.

nonconvulsive **—** any type of seizure that does not include violent muscle contractions.

***nonepileptic seizures* —** any phenomena that look like seizures but do not result from abnormal brain activity. Nonepileptic events may include psychogenic seizures or symptoms of medical conditions such as sleep disorders, Tourette syndrome, or cardiac arrhythmia. Pseudoseizure is an older term for nonepileptic seizure.

***post-ictal* —** post-seizure.

***prodrome* —** a feeling that a seizure is imminent, which may last hours or days prior to the seizure.

***progressive myoclonus epilepsy* —** a type of epilepsy that has been linked to an abnormality in the gene that codes for a protein called cystatin B. This protein regulates enzymes that break down other proteins.

***Rasmussen's encephalitis* —** a progressive type of epilepsy in which half of the brain shows continual inflammation.

***responsive stimulation* —** a form of treatment that uses an implanted device to detect a forthcoming seizure and administer intervention such as electrical stimulation or a fast-acting drug to prevent the seizure from occurring.

***seizure focus* —** an area of the brain where seizures originate.

***seizure threshold* —** a term that refers to a person's susceptibility to seizures.

seizure triggers **— phenomena that trigger seizures in some people. Seizure triggers do not cause epilepsy but can lead to first seizures or cause breakthrough seizures in people who otherwise experience good seizure control with their medication.**

status epilepticus **— a potentially life-threatening condition in which a seizure is abnormally prolonged. Although there is no strict definition for the time at which a seizure turns into status epilepticus, most people agree that any seizure lasting longer than 5 minutes should, for practical purposes, be treated as though it was status epilepticus. Repeated seizures without regaining consciousness between the events is also considered a form of status epilepticus.**

sudden unexpected death in epilepsy (SUDEP) **— death that occurs suddenly for no discernible reason. Epilepsy increases the risk of sudden unexplained death about two-fold.**

temporal lobe epilepsy **— the most common epilepsy syndrome with focal seizures.**

temporal lobe resection **— a type of surgery for temporal lobe epilepsy in which all or part of the affected temporal lobe of the brain is removed.**

tonic seizures **— seizures that cause stiffening of muscles of the body, generally those in the back, legs, and arms.**

***tonic-clonic seizures* —** seizures that cause a mixture of symptoms, including loss of consciousness, stiffening of the body, and repeated jerks of the arms and legs. In the past these seizures were sometimes referred to as *grand mal* seizures.

***vagus nerve stimulator* —** a surgically implanted device that sends short bursts of electrical energy to the brain via the vagus nerve and helps some individuals reduce their seizure activity.

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Prepared by:

Office of Communications and Public Liaison
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20892

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