



EPILEPSY

A GIVING SMARTER GUIDE



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EXECUTIVE SUMMARY

One in twenty-six Americans has epilepsy, a condition characterized by unprovoked and recurrent seizures. At least 50 million people live with this disorder worldwide according to the World Health Organization. The manifestation of epilepsy, in terms of seizure type, severity, and age of onset, varies widely among patients. Just like there are many different cancer subtypes and severities that require tailored individualized treatment, epilepsy is beginning to be viewed as having many subtypes. Unfortunately, the biological and clinical profiles of all epilepsy subtypes are not well known. Although these profiles are difficult to elucidate, a focused effort to comprehensively identify and characterize epilepsy subtypes using precision medicine would greatly improve clinicians' ability to diagnose and treat patients based on their epilepsy type.

Thirty to forty percent of epilepsy patients do not achieve effective seizure control with currently available therapies. Those who do achieve seizure control are often left to contend with severe adverse side effects from epilepsy therapies, comorbid conditions such as depression and anxiety, sleep disorders, learning and memory problems, increased suicide risk, and public misunderstanding and discrimination. If seizures remain uncontrolled, patients often experience lifelong disability. Supporting the expansion or development of accredited epilepsy centers with coordinated medical care teams would substantially improve comprehensive holistic care.

There are no disease-modifying therapies for epilepsy. Current epilepsy medications do not treat the underlying cause of epilepsy, but instead treat seizure, which is a symptom of epilepsy. Knowledge gaps in understanding of the biological underpinnings of epilepsy are currently precluding the field from developing treatments that can correct the abnormal biology that drives the disease. These fundamental knowledge gaps, along with the high cost of clinical trials and competing priorities, have weakened the value proposition for the pharmaceutical industry to invest in the development of new epilepsy therapies that can treat the disease and not only the symptoms. Strategic philanthropic support for basic and translational research to close the aforementioned knowledge gaps could incentivize the industry to pursue novel therapeutic targets.

Epilepsy is underfunded. Compared to other neurological diseases, government funding and nonprofit support has lagged behind. For example, epilepsy is *six times more prevalent* than Parkinson's disease, but receives *10 times less funding* from nonprofit and government funding sources combined. Additional funding and opportunities to attract young investigators and to encourage collaboration among the different research communities would ensure a sustainable and thriving workforce.

The Milken Institute Center for Strategic Philanthropy has developed this Epilepsy Giving Smarter Guide with the express purpose of empowering patients, supporters, and stakeholders to make informed, strategic decisions when directing their philanthropic investments and energy into research and development efforts.

OVERVIEW

Epilepsy is a neurological condition characterized by seizures. Due to the range of differing seizure types and numerous causes, epilepsy comprises a spectrum of syndromes (referred to as the epilepsies) that affect patients and their families to varying degrees.

According to the Centers for Disease Control and Prevention, about 5.1 million people have received a diagnosis of epilepsy or a seizure disorder, making it one of the most common neurological disorders in the United States. The World Health Organization estimates that about 50 million individuals worldwide are diagnosed with epilepsy and that those at the lowest income levels bear a disproportionate burden of this disorder.

It is estimated that 60 to 70 percent of people with epilepsy can control seizures with existing treatments. However, for many of these patients, epilepsy remains a lifelong condition that requires combinations of up to six medications at a time. Moreover, the medications can have potential life-altering side effects ranging from dizziness, nausea, and fatigue to memory loss, liver toxicity, kidney dysfunction, bone loss, and brain atrophy. For pregnant woman, some medications can cause life-threatening birth defects in their unborn children. Furthermore, even though their seizures may be under control, patients often struggle with comorbid conditions such as depression and anxiety, sleep disorders, and learning and memory challenges. They are at risk of early mortality, especially from suicide, struggle for access to high-quality healthcare in neurology and other specialties, and are the victims of public misunderstanding and discrimination.

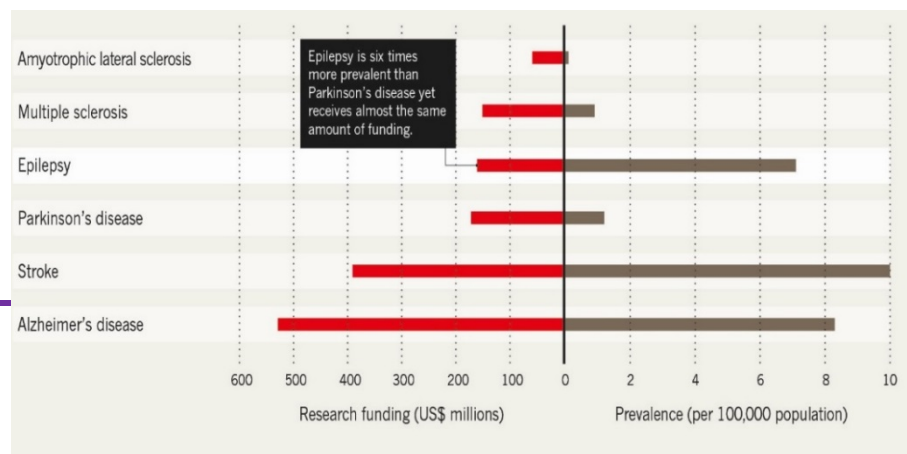
Approximately 30 to 40 percent of epilepsy patients are treatment resistant and live with uncontrollable seizures. According to an Institute of Medicine report, this group is also at a higher risk of mortality, having a 20 times higher rate of sudden unexpected death compared to the general population. The most catastrophic forms of epilepsy occur in very young children and have a lifelong negative impact on patients, families, and communities.

The ultimate goal is to develop better therapeutics that eliminate seizures and side effects for all people living with epilepsy.

SOCIETAL IMPACT OF EPILEPSY

Although epilepsy is a physical disorder of brain function, it often carries with it a substantial social burden that includes unemployment and uncertainties about future employment, low income and social isolation. Moreover, there can be questions about independent living, driving limitations, and stigma for those whose seizures can be managed, and debilitating, lifelong disability for those whose seizures cannot be controlled. One-third to one-quarter of children diagnosed with epilepsy will have an associated intellectual disability or learning disorders. Furthermore, people with epilepsy are three times more likely to commit suicide compared to the general population. The risk for suicide increases to fivefold among newly diagnosed patients.

The total direct and indirect costs of epilepsy in the United States is about \$19.7 billion per year. This estimate is based on a



total cost of \$12.5 billion calculated in 1995 and converted to 2016 dollars using Bureau of Labor Statistics data.

Although epilepsy is among the most common neurological disorders and its associated economic costs are high, United States government investment in epilepsy research is modest. Funding for epilepsy has lagged behind that for other common neurological conditions. For example, epilepsy is six times more prevalent than Parkinson’s disease and multiple sclerosis, but the three diseases receive similar amounts of funding (see Figure 1).

CHARACTERISTICS OF EPILEPSY

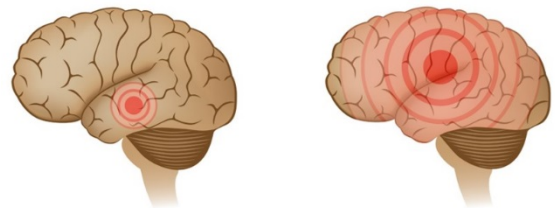
The nerve cells in our brain communicate through electrochemical inputs. When this communication is disrupted by sudden intense bursts of electrical energy, a person experiences a seizure. Depending on where the disruption in communication occurs, the seizure manifests itself through a range of sensations, behaviors, movements, and/or loss of consciousness

that differ in severity and frequency. Seizures can be non-convulsive and

convulsive. Typically, a seizure will last from a few seconds to a few minutes. Prolonged seizures or clusters of seizures increase the risk of permanent brain damage. Therefore, a convulsive seizure that lasts longer than 5 minutes is deemed to be a serious medical emergency and is termed **Status Epilepticus**.

One out of 10 individuals will experience at least one seizure in their lifetime. A seizure is an event, while epilepsy is a disease that involves recurrent unprovoked seizures. One in 26 Americans has or will develop epilepsy.

Figure 1. Government funding for epilepsy compared to other common neurological disorders (figure reprinted with permission from Macmillan Publishers Ltd: Nature, 2014). Source.



Focal Seizure

Generalized Seizure

TYPES OF SEIZURES— FOCAL VS. GENERALIZED

There are many different types of seizures, but they can be grouped into two broad categories: focal versus generalized. Generalized seizures result from abnormal seizure activity occurring on both sides of the brain over large areas, while focal seizures (previously called partial seizures) result from abnormal activity in just one area of the brain (see Figure 2).

Figure 2. Side view of brain with the red bull’s eye indicating the source of seizure. A focal (partial) seizure can be pinpointed to one location vs. a generalized seizure, which cannot be localized to one specific location. (Adapted from © Alila07 | Dreamstime.com. Partial and Generalized Epilepsy Photo). Source.

Generalized Seizures

Generalized seizures are disruptions in the brain network that involve both sides of the brain and can result in loss of consciousness, falls, or massive muscle contractions. These types of seizures are further classified into six categories:

- **Absence:** In an absence seizure, the person “spaces out” for a short period of time. Unlike daydreaming, these seizures can occur during physical activity and cannot be interrupted. These seizures are most commonly seen in children ages 4-14 years.

- **Atonic:** In an atonic seizure, a muscle (or muscles) suddenly loses strength. These seizures are sometimes called drop attacks because the person seizing may suddenly drop something or fall to the ground. These seizures are often brief, but, depending on where and how the person falls, serious injury can occur. This seizure is most often seen in childhood-onset epilepsies.
- **Tonic:** In contrast to an atonic seizure, in a tonic seizure, the muscle increases in tone and the body or limbs make sudden stiffening gestures. These seizures are commonly observed during sleep and usually last fewer than 20 seconds.
- **Clonic:** Clonic seizures are repeated rhythmic jerking movements of the arms and legs, sometimes on both sides of the body, which cannot be stopped by restraint. Pure clonic seizures are rare to observe, and often are seen with other seizure types.
- **Myoclonic:** Myoclonic movements are brief, shock-like jerks of a muscle or group of muscles that usually last 1-2 seconds. Many individuals have experienced a myoclonic movement or jerk when hiccupping or falling asleep. In epilepsy, myoclonic seizures usually cause abnormal movements on both sides of the body at the same time.
- **Tonic-Clonic:** This is the seizure type most often portrayed in media and was previously called a grand-mal seizure. The person seizing will lose consciousness and fall. The muscles stiffen (tonic aspect) and then jerk (clonic aspect). The seizure is also associated with a “cry” as the diaphragm muscles contract and the air in the lungs is exhaled. These seizures usually last 1-3 minutes and require a longer recover period.

Focal Seizures

Around 60 percent of people living with epilepsy will have focal seizures, which are localized to a specific focal area on one side of the brain. The type of focal seizure is often described by the area in which it originates. Depending on where the seizure is localized, it can manifest in different ways, ranging from motor, sensory, autonomic, or psychic symptoms. If areas involved in alertness and awareness are impacted, then loss of consciousness may occur.

The types of seizure symptoms are as follows:

- **Motor Focal Seizures:** These seizures impact muscle activity on one side of the body, resulting in abnormal stiffening or jerking movements of a limb.
- **Sensory Focal Seizures:** These seizures impact the senses. People may smell or taste things that are not there, hear ringing, see a spot of light, or feel a numb sensation.
- **Autonomic Focal Seizures:** These seizures impact the parts of the nervous system that automatically control body functions, resulting in strange stomach sensations, changes in heart rate/breathing, goose bumps, and sweating.

- **Psychological Focal Seizures:** These seizures impact how people think or experience events, resulting in suddenly feeling a range of emotions such as fear or happiness without reason or experiencing difficulties with memory or understanding of language. Some psychic seizures result in the feelings of déjà-vu (i.e., “I have experienced this before”) or jamais vu (i.e., “I have never been here even though the setting is actually familiar”).

A focal seizure may spread to the other side of the brain to become a generalized seizure. These events are termed as **secondarily generalized seizures**.

SEIZURE TRIGGERS

Some seizures are more likely to occur in certain situations. Factors that precipitate a seizure in an epilepsy patient are known as seizure triggers. A seizure trigger can vary by patient but should precede a seizure fairly consistently. Patients are advised to keep a seizure diary to help to identify their seizure triggers.

Examples of seizure triggers include but are not limited to the following:

- Sleep cycle
- Sleep deprivation
- Stress
- Alcohol/drug use
- Hormonal changes (often related to the menstrual cycle)
- Illness, especially in children with epilepsy

EPILEPSY SYNDROMES

Epilepsy can be further characterized by many features other than the type of seizure observed, such as the age of onset, whether or not the seizures occur during sleep or awake states, what type of electrical activity is recorded from the brain during the seizure, and whether there are accompanying mental, physical, or psychological conditions. Currently, more than 30 epilepsy syndromes have been identified (see Appendix for more details).

EPILEPTIC ENCEPHALOPATHIES

When the seizures themselves contribute to the cognitive and behavioral impairments observed, the syndrome is categorized as an epileptic encephalopathy. Various syndromes fall under this category, but they begin in pediatric populations and are often unresponsive to available therapies. Therefore, they carry the lifelong prospect of disability and reduced quality of life. Epileptic encephalopathy is a major area of focus for improving epilepsy treatment and quality of care.

SEIZURES NOT ASSOCIATED WITH EPILEPSY

Having a seizure does not mean that a person has epilepsy. Common examples of seizures that are not necessarily epilepsy include

- **Febrile Seizures:** These seizures may occur in children with high fevers.
- **Eclampsia:** This life-threatening condition occurs in pregnant woman and is associated with high blood pressure.
- **Non-epileptic events:** Some events look behaviorally as if they are seizures, but they are not due to abnormal brain signaling and therefore should not be treated with anti-seizure medications. Often called psychogenic non-epileptic seizures (PNES), these events are treated through cognitive behavioral therapy. About 20 percent of patients who are not responsive to epilepsy medication and are admitted to an Epilepsy Monitoring Unit have PNES.

CAUSES AND RISK FACTORS

CAUSES OF EPILEPSY

In general, epilepsy and seizures result from abnormal circuit activity in the brain. Therefore, any event ranging from faulty wiring during brain development to brain inflammation due to physical injury or infection can lead to seizure and epilepsy. The underlying causes for epilepsy can be stratified into the six categories listed below, all of which are explained in more detail in the following sections:

1. Genetics
2. Brain structure abnormalities
3. Metabolism changes
4. Immune system abnormalities
5. Infectious disease
6. Unknown causes

GENETICS

Currently, 2 percent of epilepsy cases have a known genetic cause, which does not necessarily mean that the genetic mutation was inherited. Many of the causative gene variants identified, especially in the severe childhood epilepsies, are due to spontaneous new mutations that arose during fetal development. The [CURE Epilepsy Genetics Initiative](#) has so far reported that 71 gene mutations are directly linked to epilepsy, 50 of which are linked to epileptic encephalopathy (i.e., severe epilepsy in children). The implicated genes are important for brain development, neuronal migration, or neuronal channel function.

Various studies have revealed that the number of genes that do not directly cause epilepsy but confer a high risk for developing epilepsy jumps from 71 to the high hundreds. This finding implies that genetics may play a much larger role in epilepsy than previously assumed. Researchers estimate that between 20 to 50 percent of all epilepsy cases may be genetically linked. Current genetic initiatives are improving their data analysis techniques to better understand the role that these genes may play.

Furthermore, some studies suggest that some genetic mutation causing the epilepsy may be somatic, that is, it occurs in a specific organ of the body. For example, a somatic gene mutation in the brain cannot be easily identified unless the brain tissue is studied directly. Some researchers are beginning to store brain tissue from neurosurgery biopsies to determine how common a somatic gene mutation is in the general population compared to individuals who undergo surgery for epilepsy.

Ideally, in the future, clinician will be able to use a patient’s genetic information to identify the genetic root cause of the seizures and develop a customized treatment plan. Known as **precision medicine**, this approach is expected to play a large role in the future treatment of genetic epilepsies.

METABOLIC ABNORMALITIES

Metabolites are molecules that are byproducts of the various chemical reactions occurring in the body. If they do not occur properly in the brain, these reactions can affect signaling, which may lead to unprovoked seizures. An example of a metabolic abnormality observed in some epilepsy patients is an underlying disturbance in sugar levels in the brain known as Glut1 deficiency syndrome. Along with many other metabolic abnormalities associated with epilepsy, this syndrome is often also associated with a specific genetic defect. Understanding the metabolic drivers of epilepsy is an important and active area of investigation among researchers, because these metabolic abnormalities present opportunities to develop targeted therapies against these defects.

BRAIN STRUCTURE ABNORMALITIES

Well-recognized brain structure abnormalities are associated with certain epilepsy syndromes. The underlying basis for structural abnormality may be genetic (e.g., malformations of cortical development) or acquired (e.g., stroke or head trauma). Abnormalities can be visualized using structural neuroimaging scans generated by computerized tomography (CT) or magnetic resonance imaging (MRI). Identification of abnormalities may indicate whether surgery is a viable course of treatment to prevent future seizures.

IMMUNE SYSTEM ABNORMALITIES

Recently, some epilepsies have been linked to autoimmune diseases and require treatment with targeted immunotherapies. Diagnoses of these autoimmune diseases are rapidly increasing in response to the improved ability to test for auto immune–induced inflammation of the central nervous system. These autoimmune diseases are often detected by collecting and analyzing cerebral spinal fluid (CSF).

INFECTIOUS DISEASE

Certain infectious diseases can cause meningitis (i.e., inflammation of the membranes surrounding the brain) or encephalitis (i.e., inflammation of the brain), which, in turn, can result in unprovoked seizures. Viral infections are the most common cause of brain inflammation. Sometimes, infection causes scarring in the brain and therefore a structural correlate that can be observed by imaging. In low-income countries, Cysticercosis, a parasitic tissue infection caused by the tapeworm *Taenia solium*, is a major, preventable cause of adult onset seizures.

UNKNOWN CAUSE

Today, the majority of epilepsy cases cannot be linked to a known cause (see Figure 3). The extent to which a cause can be identified depends on the diagnostic tools available at the treating facility. Unfortunately, diagnostic methods and access tools can vary

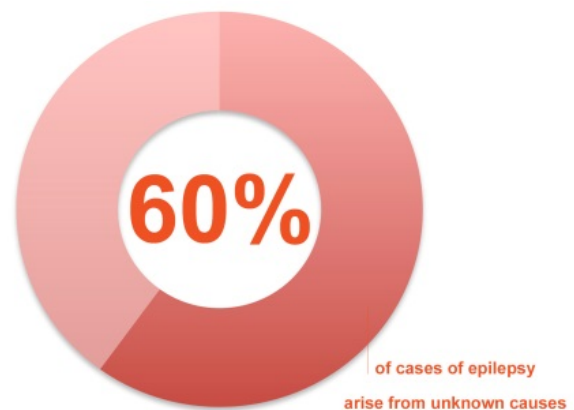


Figure 3. The majority of epilepsy cases have no known cause

significantly among healthcare settings. Many researchers suspect that epilepsies of unknown cause could be due to an undiscovered genetic defect. Several ongoing initiatives are collecting and analyzing genetic information from individuals living with epilepsies of unknown cause to better understand disease development and to evaluate therapeutic options.

RISK FACTORS

In relation to the aforementioned causes of epilepsy, key risk factors increase the likelihood of developing epilepsy. Because seizures are defined by abnormal electrical signaling between nerve cells in the brain, any event that influences how the brain communicates with itself can affect the risk for developing recurrent seizures. Therefore, head injuries, stroke, and brain infections, which can impact brain function, are risk factors for developing epilepsy.

Other general risk factors include but are not limited to:

- **Age:** Although epilepsy can occur at all ages, the prevalence is highest in children under the age of 2 and in adults over the age of 60.
- **Family History:** If a close relative has a history of recurrent seizures, then a person's risk for developing epilepsy slightly increases by two- to four-fold compared to the general population.
- **Psychiatric Disorders:** Depression, anxiety, and other psychiatric disorders are common among people with epilepsy compared to the general population. Some of the difficulties of living with epilepsy could explain this finding. However, in studies that control for the effects of living with a chronic disease, the higher risk of psychiatric disorders in epilepsy persists. Although we don't yet understand why this is the case, those with psychiatric disorders such as depression are also at higher risk for developing epilepsy.

DIAGNOSIS

Originally, the official clinical diagnosis of epilepsy was limited to two or more unprovoked seizures occurring greater than 24 hours apart.

In 2014, the clinical definition for epilepsy was expanded include

- Individuals with reflex seizures, which is triggered by a specific external stimulus such as a flashing light or a specific sound.
- Individuals with one unprovoked seizure and a **high likelihood of having another unprovoked seizure**. An unprovoked seizure has no immediate connectable cause, such as alcohol, fever, or low sugar levels. These patients were added to the definition to ensure healthcare coverage immediately after the first seizure.

Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome and outgrew their seizures or remained seizure-free for at least 10 years and were off seizure medications for at least 5 years.

FACTORS CONSIDERED FOLLOWING FIRST SEIZURE

One seizure does not mean that an individual has epilepsy. The chance of seizure recurrence increases when the following are observed:

- Prior brain injury or brain inflammation in the medical history
- Abnormal electrical brain activity as measured by electroencephalography
- Significant brain-imaging abnormality
- Nocturnal seizures

According to new 2015 guidelines from the American Neurological Association, if any of the above factors are observed after one seizure, then the doctor and patient should discuss initiation of epilepsy treatment.

RECORDING ELECTRICAL BRAIN ACTIVITIES

Recording brain pattern activity can help a clinician to determine the person's epilepsy type and best treatment.

Electroencephalography (EEG) is the technique used to record brain electrical activity (see Figure 4).

During this diagnostic procedure, electrodes attached to an EEG machine are placed on the scalp. These electrodes allow the technician to observe the activity from the different areas

in the brain under the electrodes. The detected activity is recorded as a series of traces on the EEG machine. Each



Figure 4. A 27 year old woman undergoing an EEG, or electroencephalogram, to monitor the electrical activity of her brain. An adult epilepsy diagram is shown on the screen. Credit: AJPhoto / Science Source. [Source](#).

trace represents the area of the brain under that specific electrode. During a seizure, the EEG picks up the abnormal cell signaling as abnormal traces, which often look like spikes or sharp waves. In a typical individual, the number of electrical pulses from the brain is approximately 80 per second. During a seizure, the number of pulses can increase to up to 500 per second.

Although an EEG is a helpful diagnostic tool, it is not without limitations. Although in some epilepsy syndromes, the EEG signal is abnormal even when a person is not experiencing a seizure, there are many epilepsy syndromes where the EEG is normal when a person is *not* experiencing seizures. If no behavioral seizures are observed during the EEG recording, the results may be difficult to interpret. Furthermore, EEG technology can detect only seizures that begin in, or reach, the surface of the brain. Very deep brain seizures cannot be detected by an EEG.

OTHER CLINICAL TESTS

The doctor may order other tests in addition to the EEG to attempt to determine the underlying cause. For example, the doctor may order a brain imaging scan for structural abnormality, a blood test for certain metabolic disorders, or a genetic test to confirm genetic epilepsy. Because these tests solely address potential underlying causes, normal test results do not mean that epilepsy is not present.

THE MECHANISMS OF SEIZURES

Neurons are nerve cells responsible for processing and transmitting information through electrical and chemical signals. Neurons communicate in a series of networks, which create brain circuits that control every aspect of behavior ranging from movement to awareness.

Within this neuronal network are excitatory and inhibitory neurons. As the name implies, when excitatory neurons are stimulated, they *excite* other neurons in the network to which they are connected. Conversely, when inhibitory neurons are stimulated, they *inhibit* other neurons in the network to which they are connected. One can imagine these neurons as traffic light signals. An excitatory neuron will tell its neighboring neuron to go, while an inhibitory neuron will tell its neighboring neuron to slow down or stop.

During a seizure, neurons in the network undergo massive excitation, misfire in unison, and produce intense bursts of electrical impulses known as electrical storms. These electrical storms cause a short circuit in the neuronal network, producing a wide range of observed behaviors depending on which brain circuit was disrupted.

Seizures are ultimately a breakdown in the mechanisms that normally restrain neuronal excitability. They occur when the balance between inhibition and excitation in the network is askew (see Figure 5).

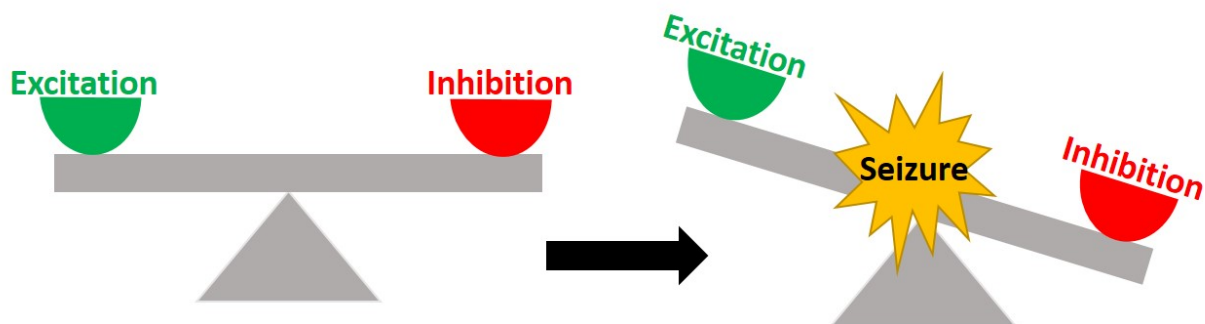


Figure 5. Imbalances between excitation and inhibition in the brain leads to a seizure.

IMBALANCES IN BRAIN CIRCUIT ACTIVITY

There are multiple ways in which the balance between excitation and inhibition could go awry. Based on genetic studies in humans and animal models, researchers postulate that imbalances in brain circuit activity leading to a seizure are usually due to the following:

- Ion channel dysfunction or
- Impaired inhibitory/excitatory neurotransmitter signaling.

ION CHANNELS

Chemicals in the body, known as **ions**, are “electrically charged” as positive or negative. **Ion channels** sit within largely impenetrable membranes that surround a neuron. As the name implies, these ion channels serve as

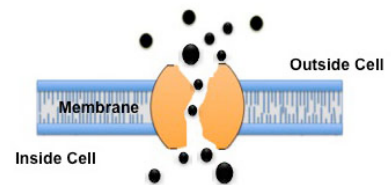


Figure 6. Ions flowing through an ion channel.

conduits, shuttling specific ions in or out of the cell depending on the ion channel type (see Figure 6).

This flow of ions in and out of the neuron creates an electrical current that determines whether the neuron is stimulated enough to fire. Therefore, faulty ion channels that let in too many or too few ions can cause neuronal firing abnormalities. **Many of the established genetic mutations linked to epilepsy syndromes occur in genes that code for these various ion channels.**

Inhibitory/Excitatory Neurotransmitter Signaling

Stimulated neurons release chemicals known as **neurotransmitters** across a small gap between two neurons called the synapse (see Figure 7). Neurotransmitters can bind to receptors on the neighboring neuron's surface. Different types of neurotransmitters are involved in brain function—some prompt the receiving neuron to carry an impulse to the next one in the series, and others inhibit the transmission of impulses.

Neurotransmitters act like a key that opens the door for closed ion channels in the membrane of the receiving neuron. Different neurotransmitters have different keys, allowing them to open specific ion channels on the receiving neuron's side. Neurotransmitters will open these channels directly through binding or indirectly through a receptor that is linked to an ion channel.

Depending on which ion channel opens, positive or negative ions flow in or out of that neuron. The resulting fluctuation in electrical charge affects whether or not the receiving neuron will continue to carry the electrical signal to the next neuron in the circuit. Excitatory neurons secrete the excitatory neurotransmitter **glutamate**, whose primary function is to excite or increase neuronal activation. It does this by opening ion channels that allow positive ions to flow into the cell, increasing the excitability of the neuron (see Figure 8, left side).

Inhibitory neurons will secrete the inhibitory neurotransmitter gamma-amino butyric acid (**GABA**), whose primary function is to inhibit or dampen neuronal activation. It does this by opening ion channels that allow negative chloride ions to flow inside the cell to neutralize neuronal activation (see Figure 8, right side).

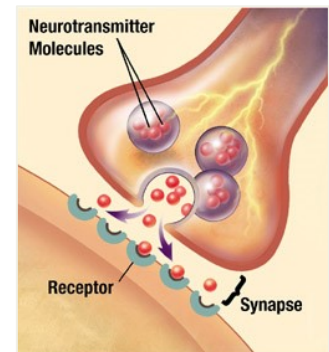


Figure 7. Neuronal communication (Image adapted from the National Institute on Aging [Public Domain] via Wikipedia Commons). [Source](#).

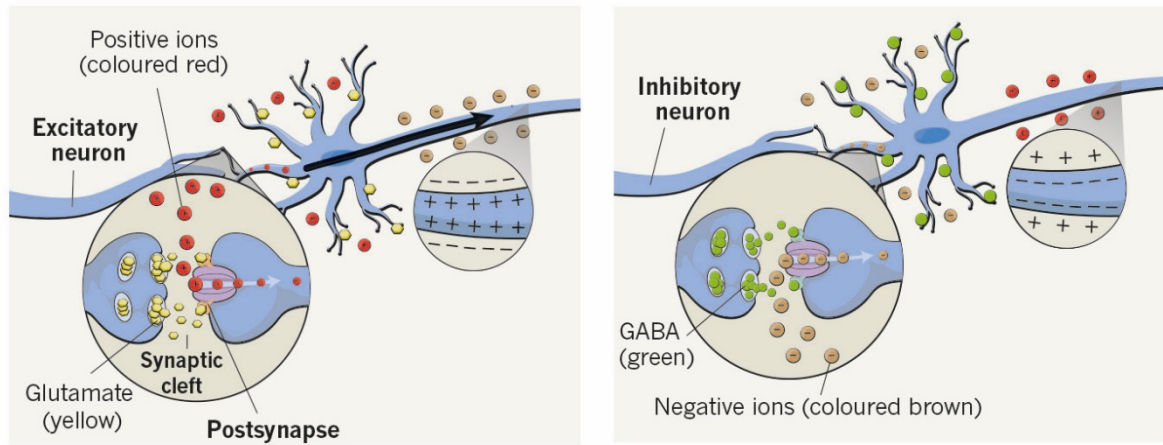


Figure 8. Excitatory vs. inhibitory neurotransmission (figure reprinted with permission from Macmillan Publishers Ltd: Nature, 2014). [Source](#).

When glutamate and GABA signaling are imbalanced, the mechanisms that normally constrain neuronal activation break down. **Both glutamate and GABA receptor mutations have been genetically associated with epilepsy syndromes.**

THE MECHANISMS OF EPILEPSY

Epileptogenesis is the process whereby a brain becomes susceptible to having recurrent seizures. Although ionic channel imbalance and impaired neurotransmitter signaling are part of the answer, they do not explain a vast majority of cases that have no clear genetic link to these molecular pathways. Something must have occurred in the brain to cause the ionic imbalance or impaired neurotransmitter signaling.

A current area of research is to better understand epileptogenesis for the purpose of designing more effective therapeutic entities that target the root cause of the disease rather than treat the outward presenting symptoms with anti-seizure therapies. This research could also lead to preventative therapies for individuals at higher risk of developing epilepsy. Genetically linked epilepsies can hint at what these mechanisms may be for a particular epilepsy or seizure syndrome, but not all epilepsies have a clear genetic association.

Recently, research on epileptogenesis has primarily focused on understanding (1) how neuronal networks develop, (2) how genetics impact abnormal network development, and (3) how certain insults to the brain, such as inflammation, can contribute to epilepsy development.

DEVELOPMENT OF NEURONAL NETWORKS

During early normal brain development, neurons migrate to precise locations and extend their processes to interact with other neurons in the network. The shape of the neuron, where it is positioned in the network, and how it interacts with its surrounding environment can influence a neuron's excitability. Understanding the factors that alter this intricate coordination to make a brain more susceptible to seizures provides insight into how seizures may be prevented.

INFLAMMATION

In a recent retrospective analysis combining patients from 66 studies, de Vries and colleagues found that a battery of inflammatory signaling molecules known as cytokines were significantly elevated in the blood, CSF, and brains of epilepsy patients compared to healthy controls. This systematic review highlights the possible role of inflammation in epileptogenesis. However, how inflammation leads to the development of epilepsy is not entirely clear. One potential explanation, however, is through glial cells.

GLIAL CELLS

Glial cells are the brain cells that help to regulate the environment around neurons. These cells buffer excess neurotransmitter levels and help to maintain proper ionic concentrations.

During inflammation, glial cells become activated. As they become chronically activated by inflammation (due to a particular brain insult such as a head injury), they may become less efficient at performing their job during epileptic states—contributing to an overall ionic imbalance and a hyper-excitable state in the brain. Active glial cells are observed in the brains of patients who have died from epilepsy, which supports this line of thought. Researchers are investigating the therapeutic targeting of glial cell regulation; however, additional human data, better disease models, and understanding of the involved inflammatory pathways are needed to clinically pursue this therapeutic approach.

TREATMENT

For most types of epilepsy, the first line of treatment is anti-seizure medications, either alone or in a variety of combinations. Strict diet modification, surgery, or neural device stimulation procedures may also be considered. Doctors will usually try 2- to 3-drug combinations before considering other options. The treatment options are explained in more detail below.

PHARMACOLOGICAL TREATMENT OPTIONS

ANTI-SEIZURE MEDICATION OVERVIEW

Anti-seizure medications are more commonly referred to as anti-epileptic drugs (AEDs). Because these drugs focus on suppressing seizures rather than targeting the underlying causes of epilepsies, the epilepsy community consider anti-seizure medications to be the more appropriate term.

Anti-seizure medications are the most commonly prescribed treatment for people with epilepsy because they are effective in controlling seizures in 60-70 percent of individuals living with epilepsy (see Figure 9). However, these drugs can cause side effects such as fatigue, dizziness, depression, and cognitive impairment. In many cases, they can interact with prescription drugs taken to combat other diseases. For example, many anti-seizure medications interact with anti-cancer medications to reduce the overall effectiveness for seizure control and tumor growth. Pregnant women must be especially careful, because some of these medications can affect the developing fetus. A primary focus in epilepsy research is to develop new medications that prevent seizures in all patients with no side effects.

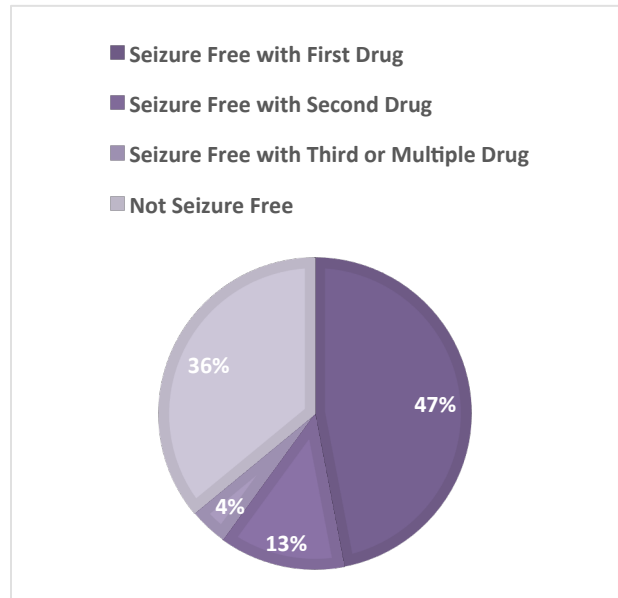


Figure 9. Percentages of epilepsy patients who achieve seizure freedom with anti-seizure drugs.

MECHANISM OF ANTI-SEIZURE MEDICATIONS

Anti-seizure medications do not treat the underlying causes of the seizure. Rather, they target the mechanisms that lead to the initiation of a seizure in an effort to stabilize the hyper-excitable neuronal network. This can be done in two ways (see Figure 10):

- Reducing the ability of excitatory neuronal cells to fire or signal, thereby reducing the excitability of the neuronal network,
and/or

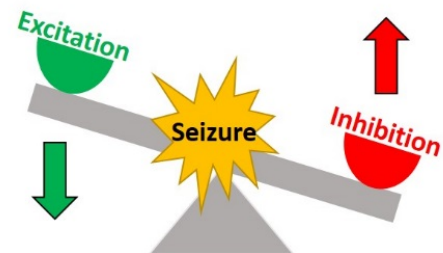


Figure 10. A seizure is an imbalance between excitatory and inhibitory signaling in the brain. Anti-seizure medications usually restore the balance between excitation and inhibition in the brain—either by reducing excitatory mechanisms or by increasing inhibitory mechanisms.

- Enhancing the effectiveness of inhibitory neuronal cells to fire, thereby increasing the inhibitory signals in the neuronal network

Because the processes that underlie excitation and inhibition are primarily driven by ion channels, neurotransmitter signaling and neurotransmitter release (see the “Mechanisms of Seizures” on p. 17 for more details), most anti-seizure medications largely target these processes. Some new drugs may target other molecules that control brain excitability. Most of the available drugs work by targeting the following:

- Sodium ion channels that are controlled by voltage levels (also referred to as Voltage Gated Sodium Channels)
- Potentiating GABA signaling, which is the inhibitory neurotransmitter that sends out a slow down or stop signal to the neuronal circuit

REDUCING EXCITATION THROUGH TARGETING VOLTAGE GATED SODIUM CHANNELS

When a neuron experiences an influx of positive ions, the voltage inside the cell becomes more positive. Voltage gated sodium ion channels open on their own at specific voltage thresholds. Sodium carries a positive charge, and there is very little sodium inside compared to outside a cell. Once these channels open, sodium pours into the cell, ensuring that the excitatory signal spreads to the next neuron. About 40 percent of anti-seizure medications work by preventing these channels from opening—therefore blunting the spread of excitatory signals in the seizure circuit.

INCREASING INHIBITION THROUGH TARGETING GABA SIGNALING

GABA is the primary inhibitory neurotransmitter in the brain. When GABA is released, it opens chloride ion channels on the receiving neuron, allowing chloride to enter the cell. Because chloride has a negative charge, the cell becomes more negatively charged as chloride rushes in. The increase in negative charge dampens the signal, and the neuron becomes less effective in sending an electrical signal to the next neuron in the series. Therefore, increasing the effectiveness of GABA signaling increases the effectiveness of inhibitory signaling to stop the excitatory signaling from the seizure from spreading to the next neuron in the circuit. Several anti-seizure medications target the GABA system by potentiating GABA signaling—either by helping GABA to keep the chloride channel unlocked and open longer, or by preventing the degradation of GABA by other biological molecules so that more GABA is available in the brain.

NON-PHARMACOLOGICAL TREATMENTS

DIETARY TREATMENTS

A classic ketogenic diet or variations of this diet may be used to treat epilepsy. According to the Epilepsy Foundation of America, approximately 50 percent of children who are placed on this diet will experience at least a 50 percent reduction in their seizures; however, it is not altogether clear why this diet is helpful. This is an active area of research.

A classic ketogenic diet is high-fat and low-carbohydrate with a restricted caloric intake. Usually, the body uses carbohydrates (e.g., sugar, bread, pasta) for fuel. When a diet is low in carbohydrates, fat becomes the primary fuel. The fat is broken down into **ketones**, which are used as the fuel substitute. In this diet, 90 percent of calories

come from fat, compared to a normal diet with 35 percent of calories from fat. This diet is extremely difficult to maintain due to its unpalatability. Moreover, this diet can cause short-term side effects such as constipation and nausea. Longer-term side effects include increased risk of bone fractures and kidney stones. To increase the diet's palatability and reduce side effects, clinicians have implemented three variations of the diet.

- **Modified Atkins Diet:** Unlike the classic diet, this diet has no fluid or calorie restrictions.
- **Medium Chain Triglyceride Ketogenic Diet:** This diet allows the individual to eat more carbohydrates than allowed by the classic diet and modified Atkins diet. Normal dietary fats consist of long- and medium-chain triglyceride fats. Long-chain triglyceride fats are not as good at breaking down into ketones compared to medium-chain triglyceride fats. By only eating fats that are efficient at extracting ketones, a person can consume more proteins and carbohydrates.
- **Low Glycemic Index Treatment (LGIT):** This variation of the classic ketogenic diet allows individuals to eat carbohydrates with a low glycemic index, which do not induce sugar levels to rise as high as other carbohydrates.

BRAIN SURGERY

Surgery is considered for epilepsy patients whose seizure onset can be clearly defined to a specific area of the brain. For some patients, brain surgery has been shown to be safer and superior than continuing an ineffective medication regime. The surgery's low complication rate of only 3-5 percent and almost no mortality suggest that it is a safe procedure. There are two types of surgeries:

- During a **resection**, the surgeon removes the area of the brain that causes seizures, which can lead to a cure if successful. This approach is not viable for patients whose seizures originate in areas of the brain that are essential for executive function, such as language or motor skill control.
- During a **disconnection**, the surgeon disrupts nerve pathways, interrupting the spread of seizures, without removing brain tissue. This approach is used when the seizures originate in essential areas of the brain. A common example of disconnection in epilepsy surgery is a corpus callosotomy, whereby the surgeon cuts the fiber bundle running across the corpus callosum (i.e., the area of the brain that connects the two sides of the brain). Often the cut is incomplete—disrupting approximately two-thirds of the fiber bundle—which inhibits the seizure's spread from one side of the brain to the other. Disconnection surgeries provide relief from, but do not generally cure, seizures.

Surgery Techniques Used

Despite the low complication rates, patients are hesitant to undergo brain surgery because of its invasive nature. However, improved techniques are making these surgeries less invasive. For example, the newest technique, Visualase, employs laser thermal ablation. A laser fiber is guided to the predefined abnormal brain tissue through a small hole in the patient's skull. The laser then heats and destroys the focal area, leaving the surrounding tissue unharmed. Another technique under investigation employs focused ultrasound, which ablates tissue in the focal area using concentrated sound waves.

NEURAL STIMULATION USING MEDICAL DEVICES

Medical device implantation is considered when the seizures cannot be controlled with existing medications and brain surgery is not a viable option. Currently, the U.S. Food and Drug Administration (FDA) has approved two devices.

The **Vagus Nerve Stimulation (VNS) device** helps to short-circuit seizures by stimulating the vagus nerve. The vagus nerve travels between the lower part of the brain through the neck to the chest and abdomen. A pacemaker-like device, the VNS device is implanted in the chest wall and a wire runs from it to the vagus nerve in the neck (see Figure 11). The device stimulates the vagus nerve by providing steady pulses to the nerve. Older VNS devices intermittently stimulate the vagus nerve, whereas newer devices stimulate the nerve when rapid heart rate is detected, a characteristic that often accompanies seizures.

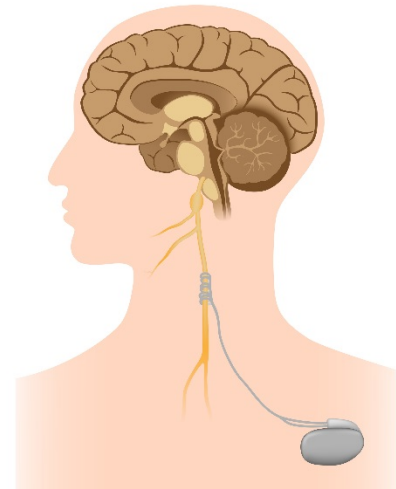


Figure 11 Vagus Nerve Stimulation Therapy (© Alila07 | Dreamstime.com).
Source.

Studies suggest that the VNS device can reduce seizure frequency by at least 50 percent in one-third of patients. Side effects occur in more than 5 percent of patients and include difficulty breathing, hoarse voice, and vomiting.

The exact mechanism by which vagal nerve stimulation controls seizures is unclear, but the theory is that stimulation of the vagus nerve also stimulates the brain, thereby interrupting the seizure circuit. Another theory is that stimulation of the vagus nerve releases factors that deter the oncoming seizure.

The **Responsive Neurostimulation (RNS) Device** is an FDA-approved device that has been on the market since 2013. This device is usually reserved for severe cases of epilepsy that are not responsive to pharmacological treatments. Clinical trial data used to support the device's approval in 2013 showed that this treatment reduces seizure frequency by 44 percent in one-half of patients.

The device consists of a microcomputer that is embedded in the skull and electrodes that are implanted directly into the predefined seizure foci region of the brain. The microcomputer monitors brain signals from the electrodes and sends electrical pulses through the electrodes to the brain in response to aberrant electrical signals to disrupt the seizure circuitry. Brain electrical activity is wirelessly uploaded in real time to a patient data management system, which enables the physician to modify the overall treatment plan as necessary.

SEIZURE-DETECTING DEVICES

A seizure alert device helps to notify others that a seizure is occurring, which is critical to preventing SUDEP (sudden unexpected death related to epilepsies) by ensuring that individuals receive immediate care during severe seizures. These devices have been developed in various hospital monitoring units and home settings, but none has been FDA approved.

These devices primarily work as motion detection devices and fall under three categories:

- **Mattress Devices** are placed under a mattress and detect vibrations.
- **Wearable Devices** are wristwatches, patches, or sensors with accelerometers or other biosensors, which detect repeated movements.
- **Camera Devices** record audio and video from a remote infrared video camera. The recordings are sent to a smart phone, which analyzes them for seizure-like activity.

In all cases, when abnormal movement is detected, an alarm sounded to alert caregivers that a seizure is occurring.

NEW-SEIZURE DETECTING DEVICES IN DEVELOPMENT

New seizure-detecting devices under development incorporate the traditional motion detection devices with other physiological measures, such as heart rate, skin conductance, and/or electrical activity produced by muscle contractions. These physiological changes sometimes precede a seizure and warn the individual to lie down or take a rescue medication. These devices are currently being tested in hospital settings. The ultimate goal is to verify these devices through clinical trials and transfer them to home settings for use.

SEIZURE DOGS

Seizure dogs have been trained to either alert the caregiver directly or activate a pre-programmed device to alert caregiver when a child is having a seizure. Some seizure dogs are also trained to place their body between the seizing child and the floor to break the fall.

CLINICAL TRIALS AND INVESTIGATIONAL THERAPIES

Clinical trials are research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, biologics, medical devices, and dietary therapies. In order to obtain FDA approval for use in human patients, a new treatment must undergo a series of clinical trials from a small-scale Phase I study on safety and dosage to a large-scale Phase III study on efficacy and adverse effects (see Figure 12). Although a critical step in the therapeutic development process, traditional clinical trials require substantial resources. On average, it takes \$37 million and 5 to 7 years to complete the first three phases of a

clinical trial. The FDA sometimes designates certain drugs that target rare diseases (such as rare epilepsy disorders) an Orphan Drug Status or Fast Track Status. The **Orphan Drug Status** provides tax incentives, waived FDA fees, and protocol assistance to pharmaceutical companies developing a drug for a small patient population, as well as extended market exclusivity rights. The **Fast Track Status** is designed to expedite the review of drugs that fill an unmet medical need.

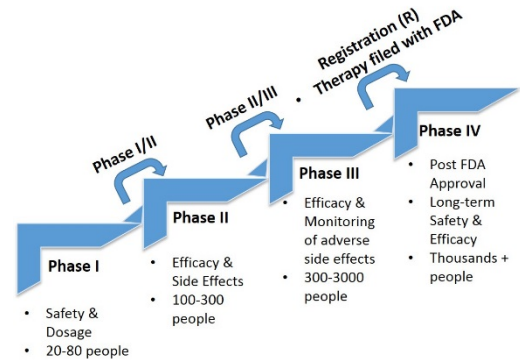


Figure 12. Clinical trials overview.

EPILEPSY CLINICAL TRIALS

As of August 2016, 80 active interventional clinical trials are evaluating treatments for epilepsy. The potential interventions include small molecule drugs, dietary modifications, and medical devices. Of these 80 trials, 31 are testing new experimental agents, including new small molecules designed to alleviate seizure frequency and duration. Figure 13 illustrates the distribution of these trials by phase.

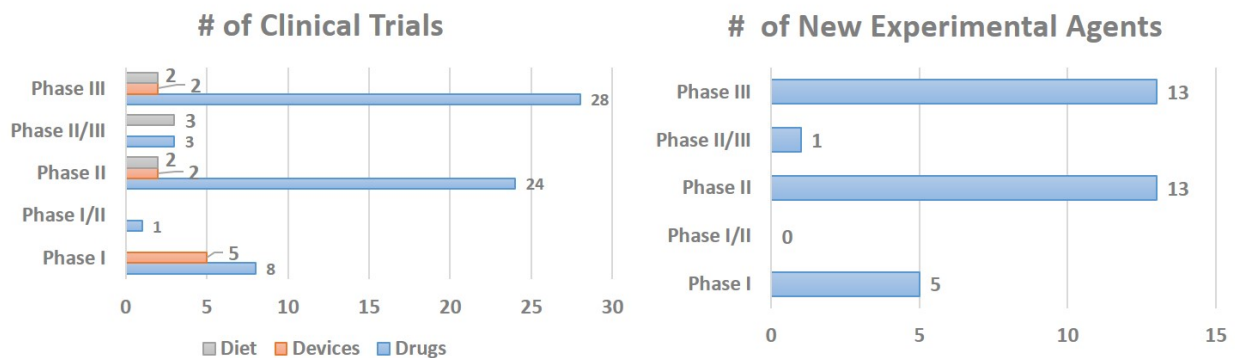


Figure 13. (Left) The number of active, interventional trials for epilepsy, by phase, currently registered at clinicaltrials.gov or BCIQ. (Right) The number of experimental agents in these interventional trials for epilepsy at each phase of development.

A more detailed discussion on the small molecules, nutraceuticals, and therapeutic devices in clinical trials is provided below.

SMALL MOLECULES IN DEVELOPMENT

The small molecules in clinical trials for epilepsy include

- molecules targeting novel molecular pathways
- molecules refining existing anti-seizure drug pathways to reduce side effects
- molecules enhancing existing drug delivery of current anti-seizure medications
- molecules reducing the risk of SUDEP

MOLECULES TARGETING NOVEL PATHWAYS

Six different mechanisms are being tested in clinical trials as potential new therapeutic targets for epilepsy.

- Serotonin
- Neuronal Gap Junctions
- Cannabidiol
- mTor
- *N*-methyl-D-aspartate (NMDA) Receptor

SEROTONIN

A neurotransmitter in the brain, serotonin is important for mood regulation, eating, and sleep. Preclinical animal models of epilepsy suggest that increasing the levels of serotonin in the brain can inhibit seizures. The mechanism for why this is the case is still unclear. Small molecules which potentiate serotonin are now being tested in clinical trials.

NEURONAL GAP JUNCTIONS

Gap junctions directly connect the inside of two cells through a passageway. Some neurons are separated by gap junctions, which allows for passage of electrical impulses. Upsher-Smith Laboratories developed a neuronal gap junction blocker that prevents the spread of activity between neurons that are linked together in this fashion. The blocker is currently in Phase II clinical trials.

CANNABIDIOL

Cannabidiol (CBD) is a non-psychoactive compound of cannabis. Historical records from as far back as 1800 BCE report cannabis as a prescribed therapeutic regimen for epilepsy. Although CBD appears to be promising, most of the data on cannabis for epilepsy treatment in the human population is anecdotal. Currently, two pharmaceutical companies (GW Pharmaceuticals and INSYS Therapeutics) have different CBD molecules in clinical trials for Dravet and Lennox Gastaut syndromes (two rare epilepsy syndromes). Phase III trials of Epidolex, a version of CBD made by GW Pharmaceuticals, for the treatment of Dravet syndrome in children have been completed and are under review by the FDA. Please note that non-pharmaceutical grade cannabis products in states that have legalized marijuana have varying levels of CBD in their strains (from 2 to 30 percent) compared to Epidolex, which contains purified plant extract with CBD content to 98 percent, or the pure CBD chemically synthesized by INSYS. The mechanism of action for how CBD works in these syndromes is not entirely clear.

MTOR

mTOR is a signaling molecule important for cell growth and proliferation. The mTOR pathway is overactive in patients with tuberous sclerosis (TS), a rare genetic disease that causes benign tumors to grow in the brain and other vital organs. The growth of these brain tumors lead to seizures and the development of epilepsy. Everolimus and rapamycin are FDA-approved drugs that suppress mTOR activity. Specifically, the drugs are approved for cancer treatment to prevent organ transplant rejection. In 2012, the FDA approved Everolimus for treatment of subependymal giant cell astrocytoma (SEGA) associated with TS. Evidence suggests that Everolimus reduces seizure frequency in individuals with TS independently of tumor growth control. Current clinical trials are testing whether Everolimus can prevent seizures in other epilepsies associated with brain abnormalities such as Focal Cortical Dysplasia.

N-METHYL-D-ASPARTATE RECEPTOR

Some epilepsy subtypes have a genetic mutation in a subtype of the *N*-methyl-d-aspartate (NMDA) receptor known as NMDA2B. The mutation causes the cells to become over excited, upsetting the balance of inhibition and excitation throughout the neuronal network. A current clinical trial is testing whether blocking NMDA2B receptors could treat the seizures observed.

MOLECULES REFINING EXISTING ANTI-SEIZURE DRUG PATHWAYS TO REDUCE SIDE EFFECTS

Researchers are developing drugs that target the same molecular pathways as currently approved epilepsy drugs; however, they aim to offer improvements with respect to side effects. Anti-seizure medications that target many different pathways are sometimes known as “dirty drugs” because they likely have unintended side effects. To reduce potential off-target side-effects, researchers are refining molecules to increase their specificity to one particular molecular target.

MOLECULES ENHANCING EXISTING DRUG DELIVERY OF CURRENT ANTI-SEIZURE MEDICATIONS

Status epilepticus may result in permanent brain damage if the seizure is not stopped as quickly as possible. Therefore, increasing the speed of delivery of anti-seizure medications to the system is critical.

Drug delivery can be enhanced by modifying existing anti-seizure medications from pill form to nasal spray form. A must be processed in the gut before entering the blood stream and subsequently the brain. A nasal spray bypasses the gut, making the route of administration quicker. Currently, intranasal or intravenous forms of oral drugs are being tested in clinical trials.

MOLECULES REDUCING RISK FOR SUDEP

SUDEP may be due to respiratory problems during the seizure that result in a cardiac arrest. Some researchers hypothesize that the respiratory dysfunction arises from a massive release of endogenous opioids following a generalized tonic-clonic seizure. The medication Naloxone reverses the effects of opioids, primarily during drug overdose situations. A current clinical trial will assess whether Naloxone improves respiratory function following a tonic-clonic seizure to reduce the risk of SUDEP.

DRUG REPURPOSING OF EXISTING ANTI-SEIZURE MEDICATIONS

Several clinical trials are re-testing anti-seizure medications approved by the FDA for use with adults in children under the age of 5. Children under the age of 5 process drugs in a different manner and could experience side effects that are not observed in an adult population.

NEUTRACEUTICALS

Anecdotal evidence suggests that modified diets such as the classic ketogenic diet can help control seizures especially in pediatric populations (see “Dietary Treatments” on p. 22 for more detail). About 8 percent of all clinical trials are testing whether dietary modifications will reduce seizure frequency and duration in various forms of epilepsy syndromes.

THERAPEUTIC STIMULATION DEVICES

Currently, four therapeutic stimulation devices are being tested in clinical trials for epilepsy.

- External Vagal Nerve Stimulation
- Trigeminal Nerve Stimulation
- Transcranial Direct Current Stimulation
- Deep Brain Stimulation

EXTERNAL VAGAL NERVE STIMULATION

This device is a modification of the VNS device described in “Neural Stimulation Using Medical Devices” on page 24. Current VNS therapy requires the patient to undergo surgery, because the device is implanted in the neck to stimulate the vagus nerve directly. Because the vagus nerve also runs by the ear, this device clips to the ear externally and stimulates the nerve through the skin.

TRIGEMINAL NERVE STIMULATION

Trigeminal Nerve Stimulation (TNS) applies the same concept as VNS therapy in that it stimulates a nerve that goes into the brain to disrupt a potential seizure network. The trigeminal nerve runs from the brain to the face and is responsible for facial sensation and motor functions such as chewing. The device consists of a hand-held pulse generator and a single-use patch that is applied to the forehead. The trigeminal nerve can be stimulated through the patch on the forehead; triggering nerve fibers to send electric pulses to the brain to disrupt seizure circuit formation. This device is currently in Phase II clinical trials in the United States and is approved in Europe.

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation treatment that delivers constant low current to the brain area of interest via electrodes on the scalp. Two types of stimulation can be delivered: excitatory stimulation to increase neuronal activity or inhibitory stimulation to dampen and reduce neuronal activity. Three clinical trials in Phases I and II are examining the safety and efficacy of tDCS to disrupt seizure activity, specifically in patients with drug-resistant forms of epilepsy.

DEEP BRAIN STIMULATION OF THE ANTERIOR NUCLEUS OF THE THALAMUS

This device has been approved in Canada and in Europe for epilepsy treatment and in the United States for treatment of essential tremors and advanced Parkinson’s disease. The device is implanted in the chest cavity, and its wires snake up behind the ear to the skull, where two electrodes are embedded into the anterior nucleus of the thalamus, an area of the brain that is often involved in the brain circuit activated by seizures. The device is like a pacemaker for the brain in that it pumps steady pulses of electricity to the area disrupting seizure circuit formation. It is currently in Phase III trials for epilepsy.

SEIZURE-DETECTING DEVICES IN CLINICAL TRIALS

Currently, only Brain Sentinel is testing seizure-detecting devices in clinical trials—all in Phase III. These devices are similar to the motion detection devices described in “Seizure-Detecting Devices” on page 25.

BARRIERS TO EPILEPSY RESEARCH PROGRESS AND KEY PHILANTHROPIC OPPORTUNITIES

About 30 to 40 percent of epilepsy patients do not achieve effective seizure control with currently available therapies. Those who do achieve seizure control may experience overlooked or adverse side effects from the prescribed medication, diet, device or surgery. **The ultimate goal for the epilepsy community is to develop better therapeutics focused on holistic care, resulting in no seizures and no side effects for all patients.**

In May 2016, the Milken Institute Center for Strategic Philanthropy convened epilepsy experts to discuss the state of science relevant to epilepsy and the challenges currently impeding progress toward improved therapeutics and care. The goal of the retreat was to identify high-impact, actionable solutions where strategic philanthropic investment could accelerate progress in the epilepsy space. The experts prioritized the following as top challenges in epilepsy:

1. Inadequate precision healthcare infrastructure
2. Inefficient process for bringing new therapies to market
3. Limited resources and collaborations between preclinical and clinical researchers
4. Lack of cohesive care that addresses epilepsy associated conditions

Each challenge is discussed in detail below, along with potential philanthropic opportunities that can address these challenges and accelerate the progress of epilepsy research. Please note that the opportunities presented below are high-level representations and should be considered carefully with respect to your philanthropic goals and discussed in detail with a philanthropic advisor.

PROBLEM: INADEQUATE PRECISION HEALTHCARE INFRASTRUCTURE

Precision healthcare accounts for the individual's biological makeup and unique clinical manifestations when tailoring a course of treatment. In epilepsy, it is often unclear which of the many available therapies will have the greatest efficacy and lowest risk for adverse effects in an individual patient. This is because researchers and clinicians do not have a clear understanding of who comprises the different epilepsy subpopulations, what factors make these different populations unique, and which currently available treatments are ideal for each specific epilepsy subtype. In the current landscape, epilepsy patient data are collected by standalone initiatives that collect different information and do not integrate with one another. In addition, because most medical health record systems do not require specific terms when coding epilepsy subtypes, clinicians use different languages to describe similar conditions. For example, partial complex seizures, focal dyscognitive seizures, temporal lobe seizures, and intractable focal epilepsy might refer to the same condition under the current system. Careful definition and understanding of the biological underpinnings of epilepsy syndromes and etiologies will facilitate better therapeutic choices.

The solutions described below were identified by experts as necessary to catalyze precision health approaches in epilepsy.

SOLUTION 1: BUILD AN EPILEPSY CLINICAL DATA COMMONS PLATFORM

An epilepsy clinical data commons platform would be a centralized database for clinicians and researchers to access worldwide. This data commons would contain anonymized individual patient data such as imaging scans,

EEG recordings, genetic data, patient-reported outcomes, and general medical history. Electronic permission from patients to share such data would be incorporated into the platform. The focus would be to hone in on syndrome type, etiology, and patient response to therapy in terms of seizure control, adverse reactions, and associated conditions. Critical to this database would be the development and application of built-in analytical tools to extract and classify data meaningfully depending on the type of research being done. Such a clinical data commons would facilitate efficient data sharing and process innovation to better understand the biological and clinical profiles of the patient population.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. ***Fund consortia focused on developing data collection and analysis standards for prospective data.*** These consortia would determine which data should be collected, the data collection standards, and the analytical toolkit needed to mine the data effectively.
2. ***Fund a bioinformatics infrastructure that will allow for intra-operability between epilepsy databases.*** Following the outcome of the consortia above, the philanthropist could support the creation of a database platform as well as the technical personnel needed to ensure that the platform is optimally developed and utilized. This infrastructure would not only allow for data aggregation, harmonization, and standardization of multiple datasets but also consist of integrated analytical tools to facilitate effective data mining. This platform will enable new insights into disease subtype and treatment resistant features.

SOLUTION 2: CREATE LARGE-SCALE INFRASTRUCTURE TO SUPPORT BIOMARKER DISCOVERY USING PATIENT SAMPLES

A biomarker is an indicator of a certain state or phenomenon in the body. An ideal biomarker is a measurable dynamic change that can objectively assess disease progression and/or objectively track treatment efficacy in patients. In epilepsy, the only measure of disease progression is the severity and frequency of seizures, which occur episodically. Patients are often left not knowing if and when the next seizure will arrive. The availability of biomarkers that allow clinicians to assess the effectiveness of treatment and correct course when needed would dramatically transform care and outcomes for patients. In addition, biomarkers that can predict the likelihood of a patient to develop epilepsy would allow clinicians to target epilepsy prevention rather than epilepsy treatment. For a biomarker to be accepted as a true objective measure of a disease state or treatment efficacy, it must be confirmed by replicate experiments (biomarker validation) and detected in clinically relevant tests (assay development). The epilepsy field is still in the biomarker discovery stages and requires infrastructure to generate and aggregate biological samples on the scale necessary to support biomarker discovery research.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. ***Fund an epilepsy brain tissue repository to support biomarker discovery.*** Brain tissue removed from epilepsy patients that undergo neurosurgery is often discarded. This tissue is a valuable resource because it enables a variety of studies that could lead to the discovery of new biomarkers, patient subtypes, and/or therapeutic targets. The accompaniment of clinical data from the patient dramatically enhances the value of the tissue. Examples of clinical data include EEG recordings, structural scans, and genetic testing, all of which are collected at most epilepsy centers. There is an opportunity to standardize collection of brain tissues at epilepsy centers, centralize them in a biorepository, and provide access to samples and data to

researchers around the world. This repository would allow researchers to examine brain tissue along with the wealth of other information collected at an epilepsy center to identify changes in the brain that correspond to epilepsy subtype or disease severity. Philanthropists could support the centralized administrative core that would coordinate among the sites as well as the necessary storage equipment. Ideally, such a repository would be closely linked to the epilepsy clinical data commons platform described above.

2. **Enhance infrastructure at traumatic brain injury treatment centers.** Traumatic brain injury (TBI) is a risk factor for developing epilepsy. Patients with a TBI often receive continuous follow-up monitoring and treatment at TBI centers that collect baseline data through, for example, blood draws and structural scans. An infrastructure that would leverage these centers to also include EEG recordings and prospective follow-up may help to identify patients at risk for developing epilepsy as well as the course for disease progression. Overall, this type of infrastructure would support discovery of biomarkers for epilepsy.

SOLUTION 3: IMPROVE PRECISION DIAGNOSTIC TOOLS

Currently, clinicians rely on seizure diaries maintained by the patient or caregiver to assess treatment effectiveness. The user friendliness and convenience of these diaries have improved, in part because of mobile applications. However, it is still difficult to capture seizures in people who lose consciousness and therefore do not realize they are seizing. This unreliability is troubling because seizure diaries are the primary indicator of a drug's effectiveness. Improved diagnostic tools that would be able to detect seizures or assess whether a drug has reached its intended target would improve the clinician's ability to customize treatment to the individual patient.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. **Sponsor crowdsourcing challenges to improve seizure algorithm detection/prediction in humans.** Although seizures happen episodically, it remains difficult to predict when seizures will occur, and treatment cannot be tailored to seizure onset. The fear and uncertainty of having a seizure along with the side effects of anti-seizure medications can significantly impact a patient's quality of life. Epilepsy academicians have been developing algorithms for seizure prediction using EEG data for more than 40 years but have achieved a detection accuracy of only 65 percent. A recent 3-month crowdsourcing effort that extended the challenge to developers outside of the epilepsy field led to the design of an EEG algorithm that accurately detected seizures 84 percent of the time. Changing the culture to allow for open-sourced data and incentivizing others to join the effort accelerated the pace of research dramatically. Therefore, funding initiatives that expand upon previous crowdsourcing challenges (e.g., where EEG data is paired with wearable devices, structural scans, or medical record information) could build upon and improve existing algorithms. The ability to predict seizures would empower patients, informing them about medication timing and the need to avoid driving or other activities that place them at risk.
2. **Fund companion diagnostic tool development projects that assess an individual's response to the drug target.** Currently, there is no clinical test to determine whether an anti-seizure drug is impacting its intended molecular target. For example, there is no way to determine whether an anti-seizure medication designed to increase availability of the inhibitory GABA neurotransmitter in the brain is actually achieving this desired outcome. A diagnostic tool that compares the amount of GABA available after treatment to

control would indicate whether the drug is working on its intended molecular target (i.e., GABA). Assuming that a patient is fully adherent to the prescribed dosing regimen, these types of assays would help clinicians to determine whether a patient is not responding to treatment because the target or dose are incorrect, or because the drug is less effective in that patient because of genetics, environmental factors, co-morbidities, or other variables.

3. **Partner with industry to fund seizure-detecting device clinical trials.** Several commercial devices currently marketed as seizure alert systems have not undergone rigorous clinical testing through the FDA process. Clinicians are often reluctant to recommend their use to patients because of the uncertainty about their utility and reliability in different seizure subtypes. Although these devices have great potential, rigorous validation by FDA-sanctioned clinical trials is necessary before they will be widely embraced by the clinical community. Because the cost of conducting device trials for FDA approval can be a high barrier to biotech companies developing these devices, philanthropists could partner with industry to provide financial support for these trials.

Table 1. Summary of Potential Philanthropic Solutions to Address Inadequate Precision Healthcare Infrastructure

Potential Solutions	Corresponding Philanthropic Opportunities
Build an epilepsy clinical data commons	Fund consortia focused on developing data collection and analysis standards for prospective data
	Fund a bioinformatics infrastructure that will allow for intra-operability between epilepsy databases
Create large-scale infrastructure to support biomarker discovery using patients’ biological samples	Fund an epilepsy brain tissue repository to support biomarker discovery
	Enhance infrastructure at traumatic brain injury treatment centers
Improve precision diagnostics	Sponsor crowdsourcing challenges to improve seizure algorithm detection/prediction in humans
	Fund companion diagnostic tool development projects that assess an individual’s response to the drug target
	Partner with industry to fund seizure alert device clinical trials

PROBLEM: INEFFICIENT PROCESS FOR BRINGING NEW THERAPIES TO MARKET

Thirty to forty percent of the epilepsy patients lack effective treatment for seizure control despite the large number of commercially available drugs, many of which are generics. Unless a new drug can demonstrate a clinical efficacy superior to existing drugs or dramatically improve side effect profiles, it is unlikely that a patient will choose it. Given the high cost of clinical trials and competing priorities, industry is generally wary of pursuing new epilepsy medications because the chances of discovering a superior anti-seizure drug are low. Therefore, opportunities to lower the barriers to conducting clinical trials would encourage industry to invest in new epilepsy drug discovery and development.

The epilepsy field also needs a more robust and standardized preclinical trial infrastructure. Within the past few years, several molecular targets with potential therapeutic implications for epilepsy patients have been discovered. However, they were discovered through only one preclinical model (usually rodent models) and demonstrated in only one laboratory. For these types of discoveries to be translated into clinically meaningful results, the target must be validated using other models and replicated in multiple laboratories. Although this evidence is imperative to demonstrating the clinical relevance of the molecular target, researchers seldom receive federal funding to replicate and validate the work of others.

SOLUTION 1: CREATE A COORDINATED PRECLINICAL TRIAL INFRASTRUCTURE

The field is in desperate need of a robust and coordinated preclinical infrastructure that supports target and validation studies and assay development. A well-funded multicenter preclinical trial consortia would address many of the aforementioned challenges, ensuring that animal protocols are standardized, rapidly administered, and efficiently implemented throughout the consortia network.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. **Fund a multicenter preclinical trial consortium infrastructure.** Consortium would consist of laboratories from multiple institutions that would commit to work streams related to target verification in multiple animal models (e.g., rodent models) as well as alternative models (e.g., iPS cells or zebrafish). This infrastructure would test both new and repurposed compounds across different models in multiple labs to ensure reliability and reproducibility of potential drug targets identified in discovery stages before they enter clinical trials. Moreover, this infrastructure would ensure that animal protocols are standardized, rapidly administered, and efficiently implemented.
2. **Fund the startup costs to build an open-source library of existing compounds and the mechanisms they target.** As more is learned about the basic biology of epilepsy disorders, compounds with novel mechanisms are being considered for drug screening. The NIH/National Institute of Neurological Disorders and Stroke (NIH/NINDS) Epilepsy Therapy Screening Program (ETSP) has proposed to generate an open-source reference library of “tool” compounds that relates activity against known biological targets to activity in the program’s screening models. The goal of this effort is to determine whether these compounds (which could include drugs available for repurposing) and/or their targets show promise for further development. A philanthropist could partner with this program to support the startup costs of the platform, because funding has not been fully secured. Such an open-source library of compounds would create process efficiency and would provide preclinical proof of concept for potential promising targets

and compounds (including repurposed compounds) for further development and evaluation in clinical trials.

SOLUTION 2: IMPROVE CURRENT DRUG-SCREENING ASSAYS

Although rodent models have served as the primary basis for epilepsy drug discovery research for more than 40 years, these models are not ideal for high-throughput drug screens. Supporting initiatives that accelerate rate-limiting steps in mouse model drug platform screenings or developing, optimizing, and supporting alternative higher-throughput models would create process efficiency and expand the pipeline.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. **Fund a crowdsourcing challenge to develop improved algorithms for automated seizure detection in animal models.** Detecting seizures in preclinical animal models is a time-consuming process that requires continuous EEG recording and video monitoring to ensure that seizures are accurately detected. In turn, the analysis requires sufficient manpower to watch the recordings in real time and count the seizures by hand. Researchers agree that this analysis is the rate-limiting step in the drug discovery platform. If this process could be fully automated, then the drug discovery process would be streamlined and compounds would be screened for effectiveness more quickly.
2. **Support the development of innovative high-throughput drug platforms.** The epilepsy field offers few alternatives to traditional drug screening platforms. Moreover, a comprehensive review of what outcome measures would be clinically meaningful for patients (aside from a reduction of seizures) in traditional mouse models has not been performed. Currently the International League Against Epilepsy (ILAE) and with the American Epilepsy Society (AES) have developed a translational taskforce focused on recommending guidelines for the most pertinent data elements in preclinical models. Newer technologies, such as improved genome editing techniques (e.g., CRISPR/Cas9), allow for the development and expansion of potential alternatives (e.g., iPS cells, zebrafish) to traditional rodent models and could inform a precision medicine–based drug discovery strategy. Philanthropists could support the further development of novel high-throughput drug platform models that incorporate clinical data elements as applicable. Such an initiative would encourage and incentivize new, innovative, and clinically relevant approaches to drug discovery.

SOLUTION 3: PARTNER WITH INDUSTRY TO LOWER THE HURDLE FOR INVESTMENT IN EPILEPSY CLINICAL TRIALS

Bringing a drug to market to treat any disease or disorder is time consuming, labor intensive, risky, and costly. According to a [2013 Nature Reviews Drug Discovery article](#) on epilepsy, the average success rate of an epilepsy drug moving from discovery stages to clinical trials to FDA approval is 5 percent, with an average investment of \$350 million over 10 years. Innovating clinical trials to incentivize industry investment would have a significant effect on the clinical pipeline.

1. **Support the development of a database housing clinical trial ready cohorts for epilepsy trials.**
Traditional epilepsy clinical trials that establish a new compound’s differentiation from existing therapies are time consuming and costly. The establishment of a registry for a longitudinal clinical trial cohort of well-characterized, clinical trial–ready subjects would decrease the time and expense needed to recruit high-quality patients and measure their baseline clinical characteristics. Centralized databases of epilepsy center and hospital patient data—such as baseline seizure frequency, duration, and severity and medication history—would provide a mechanism to access subjects for studies.
2. **Support the development of novel clinical trial networks testing “proof of concept” Phase II trials.** Phase II is the riskiest stage of the pipeline, with 65 percent of drugs failing to move into Phase III trials. This phase is an important tipping point in early clinical development because it provides the evidence needed for investment in larger Phase III trials, where a significant proportion (70 percent) of the total industry investment is made. Utilizing novel clinical trial designs to evaluate multiple compounds on an ongoing basis can provide an infrastructure for efficiently and cost-effectively testing proof of differentiation for new epilepsy compounds. Examples of such clinical trial designs exist already for breast cancer (ISPY-2) and Alzheimer’s disease (EPAD), which is scheduled to start in 2017. Partnering with industry to support an epilepsy clinical trial network would provide an effective, cost-effective mechanism for proof of differentiation and would contribute to de-risking pharma’s prioritization of epilepsy and investment in the necessary and costly clinical trials.

Table 2. Summary of Potential Philanthropic Solutions to Address the Inefficient Process for Bringing New Therapies to Market

Potential Solutions	Corresponding Philanthropic Opportunities
Create infrastructure for preclinical target validation	Fund a “center without walls” grant for a multicenter preclinical trial infrastructure
	Fund the startup costs to build an open-source library of existing compounds and the mechanisms they target
Improve current drug screening assays	Fund a crowdsourcing challenge to develop improved algorithms for automated seizure detection on animal models
	Support the development of innovative high- throughput drug platforms
Partner with industry to lower the hurdle for investment in epilepsy clinical trials	Support the development of a database of clinical trial–ready cohorts for epilepsy trials
	Support the development of a clinical network for “proof of concept” Phase II trials

PROBLEM: LIMITED RESOURCES AND COLLABORATIONS BETWEEN PRECLINICAL AND CLINICAL RESEARCHERS

Regardless of the type of preclinical epilepsy research being analyzed, it must translate to clinically meaningful information in order to benefit patients. The challenge here is that basic scientists and clinicians often have limited

interaction and work in siloes, which creates a misalignment of priorities between these two communities and hinders effective translation of preclinical research.

Moreover, funding for young investigators is limited, which leaves little incentive for new investigators to remain in the field. In addition to maintaining the current workforce of epilepsy researchers, there is a need to attract scientists from other disease areas and disciplines (e.g., engineering, computer science) to cultivate new ideas and fresh research agendas. For example, attracting engineers and computer scientists to work on improving seizure detection algorithms and database interoperability could accelerate progress in these areas and have a dramatic effect on other areas of epilepsy research.

SOLUTION 1: INVEST IN HUMAN CAPITAL

Providing support for early-stage investigators and attracting new investigators to the epilepsy field will ensure that the workforce continues to grow, providing stability to the research pipeline.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. **Fund additional programs that invest in predoctoral researchers, postdoctoral fellows, and early-stage investigators.** Grants to provide fellowship stipends or bridge funding would encourage young researchers to remain in the epilepsy field. In addition, to meet the need for computer scientists and engineers, funding for specific training programs would encourage these experts to enter the epilepsy field.

SOLUTION 2: PROMOTE COLLABORATIONS

Facilitating consortia or conferences for different sectors of academia, clinical care, patients, and industry to come together would ensure that the research and development pipeline aligns with patient needs.

CORRESPONDING PHILANTHROPIC OPPORTUNITIES

1. **Fund an annual conference that brings together basic science researchers, clinicians, and patients.** An annual conference that brings together these stakeholders to discuss the epilepsy field's needs and to help focus the epilepsy community on the assays that are lacking in the space would streamline the preclinical to clinical initiatives.
2. **Provide grants for small epilepsy foundations to host scientific conferences that would ensure cross-talk between researchers and communities.** There are many foundations representing specific epilepsy subtypes. Although these foundations have strong ties to their respective patient communities, they often lack financial support. A grant mechanism that provides funds to foundations to convene researchers and patients to identify the key needs unique to the subpopulation could uncover new considerations for treatment and assay development that could be applicable to other epilepsy subtypes.

Table 3. Summary of Potential Philanthropic Solutions to Address the Limited Resources and Collaborations Among Stakeholders

Potential Solutions	Corresponding Philanthropic Opportunities
Invest in human capital	Fund additional training programs that invest in postdoctoral fellows and early-stage investigators
Promote collaborations	Fund an annual conference that brings together basic science researchers and clinicians together
	Provide grants for small epilepsy foundations to host scientific conferences that encourage cross-talk between researchers and communities

PROBLEM: LACK OF COHESIVE CARE TO ADDRESS EPILEPSY-ASSOCIATED CONDITIONS

Seizures are one symptom of epilepsy. Other associated conditions include intellectual disabilities, mood disorders, and sleep disorders. Epilepsy centers are accredited centers with coordinated teams that provide high-quality comprehensive care to epilepsy patients. These care teams consist of various specialists such as epileptologists, neurologists, neurosurgeons, neuroradiologists, genetic counselors, psychologists, psychiatrists, social workers, and dieticians. Epilepsy centers specialize in defining epilepsy subtype, which facilitates the selection of the most efficacious treatment plan. Moreover, epilepsy centers provide patients with the opportunity to participate in novel clinical trials. Because of all of these advantages, it is recommended practice to refer a patient who has failed two or more anti-seizure medications to an epilepsy center.

The requirements to sustain and support epilepsy centers can be stratified by country type:

- *Countries with epilepsy centers that are either under-utilized or could be supplemented with additional support:* Although the care teams at epilepsy centers are extensive, there are opportunities to maintain support for psychologists or social workers to help patients manage the mental health disorders associated with epilepsy and other challenges related to quality of life. Mental healthcare specialists are important because epilepsy has a strong established bi-directional relationship with depression and anxiety. However, the behavioral programs at epilepsy centers often struggle to find financial support, and therefore these specialists cannot specialize in epilepsy patient care. Moreover, less than 1 percent of epilepsy patients in the United States are referred to these centers by primary care physicians and general neurologists. Often doctors outside of the epilepsy field view these centers as primarily surgical centers, therefore not realizing that they also provide holistic care. Awareness and culture change are necessary to ensure that patients are referred to epilepsy centers as soon as possible to avoid misdiagnosis and/or a delay in administration of the most appropriate treatment
- *Countries with the medical expertise necessary to facilitate an epilepsy center but no centers within their borders:* These are often middle-income countries that have trained doctors and the basic equipment to provide care but insufficient resources to build a specialty center.
- *Countries without the professional staff and equipment required to provide minimal epilepsy care:* These are often low-income countries where telemedicine may be optimized to connect the primary care providers to international epilepsy centers for support and guidance.

SOLUTION 1: PROMOTE EPILEPSY HEALTH LITERACY AMONG THE PATIENT AND MEDICAL COMMUNITY

The goal of epilepsy centers is not to remove the primary care physician or home neurologist from the patient's care, but to partner with them to offer the best therapy to the patient. In many cases, medical professionals outside of the epilepsy field are unaware of the extent of services that epilepsy centers can provide. This issue is often resolved by educating the patient and medical communities through education campaigns.

Even when patients are referred to epilepsy centers, they can encounter logistical barriers to care such as a lack of transportation. Therefore, the opportunity exists to provide support for tele-clinics during which primary care physicians present their cases, through videoconferencing, to specialists who provide advice and clinical mentoring. This model could be expanded to countries that lack basic epilepsy care.

CORRESPONDING PHILANTHROPIC SOLUTIONS

1. **Fund an educational campaign that educates patients and medical communities about epilepsy centers.** This investment would significantly affect the quality of care that patients receive. Often doctors outside of the epilepsy field do not realize that epilepsy centers provide holistic care to the patients. An additional campaign could focus on the signs or symptoms of epilepsy that are frequently misdiagnosed or result in a delay to diagnosis.
2. **Fund a pilot tele-health epilepsy program to increase patients' access to specialty care.** This investment would address three barriers: (1) insufficient provider knowledge about appropriate epilepsy treatment; (2) transportation issues for people with epilepsy; and (3) high costs that prevent patients from obtaining care at epilepsy centers. Programs could expand upon Project ECHO (Extension for Community Healthcare Outcomes) an evidence-based model that hosts weekly tele-clinics for primary care physicians to present their patient cases to epilepsy specialists using case-based learning and video-conferencing. These interactions promote adherence to best practices, thereby reducing the variation in care. New Mexico has launched an ECHO clinic model for epilepsy care to reach underserved rural areas. This tele-clinic model could be piloted in other areas of the U.S. without epilepsy centers or specialists, as well as underserved areas abroad. Funding would be directed toward supporting a regional ECHO epilepsy clinic hub, as well as assessing the overall implementation, effectiveness, and quality of the program.

SOLUTION 2: SUPPORT EXTENSION OF STAFF AT EPILEPSY CENTERS

Ensuring that there is at least one epilepsy center per country and that each center is staffed adequately to address all patient needs, not just the seizure symptoms, will enhance the quality of care for epilepsy patients.

CORRESPONDING PHILANTHROPIC SOLUTIONS

1. **Fund international subsidies to build epilepsy centers in countries that have none within their borders.** Some countries have the professional expertise but lack the necessary equipment and infrastructure to establish a centralized specialty center for care. A philanthropist could fund grants for countries to establish such a center, promoting international access to quality epilepsy care.
2. **Fund "safety-net" subsidies for epilepsy centers to support a psychologist's or clinical social worker's salary.** Epilepsy centers often do not have the resources to hire a full-time dedicated psychologist or

clinical social worker. A philanthropist could fund grants to epilepsy centers requesting 1-year salary support for a psychologist or social worker. This approach would allow epilepsy centers to have extended staff nationwide.

Table 4. Summary of Potential Philanthropic Solutions to Address the Lack of Cohesive Care for Epilepsy-Associated Conditions

Potential Solutions	Corresponding Philanthropic Opportunities
Promote epilepsy health literacy among the patient and medical community	Fund an educational campaign that educates patients and the medical community about epilepsy centers
	Fund a pilot tele-health epilepsy program to increase patients’ access to specialty care
Support extension of staff at epilepsy centers	Fund international subsidies to build epilepsy centers in countries that have none within their borders
	Fund “safety-net” subsidies for epilepsy centers to support a psychologist’s or clinical social worker’s annual salary

OTHER INITIATIVES

Payer issues are not discussed above. As the ecosystem for epilepsy treatment changes, questions about reimbursement will arise. Specifically, if a preventative epilepsy treatment becomes available, how will health insurance companies cover the cost? In the area of value and coverage, philanthropists have limited opportunities to participate. However, potential consortia could be funded to encourage the various stakeholders such as government and industry to discuss what the future issues and opportunities.

SUMMARY

The proposals described above could greatly improve the field of epilepsy research. The Epilepsy Scientific Advisory Group identified the following proposals as the major inflection points for philanthropic support:

- **Build an epilepsy clinical data commons platform.** An overarching theme throughout the retreat was the lack of information that the epilepsy field has about its patients. Clinicians do not know with 100 percent certainty the frequency, type, intensity, timing, and precipitating factors of their patients’ seizures. A platform that collects these data and provides the appropriate analytical tools would improve a clinician’s ability to rapidly diagnose, facilitate patient stratification to get patients to their therapeutic endpoints quicker, and promote drug discovery. Such a database would also accelerate biomarker discovery and precision diagnostics through the process efficiency resulting from such a platform.
- **Invest in young investigators.** Young investigators are essential to the system’s sustainability. The field’s ability to move forward will be greatly limited if it cannot recruit and retain investigators.
- **Promote collaborations through funding conferences that bring together basic science researchers, clinicians, and patients to discuss key unmet needs.** The assays developed must be clinically meaningful. Therefore clinicians and preclinical researchers must talk to each other to ensure that drug discovery platforms and diagnostic assays are useful. Also important to this conversation is the patient, who could provide input on what should be prioritized. A small capital investment in annual conferences where

stakeholders meet in person to discuss current discoveries and unmet needs would ensure that their missions are aligned.

- **Support communication campaigns and tele-health regional hubs to increase access to quality care.** Epilepsy centers are designed to provide cohesive holistic care to the epilepsy patient. Referring patients to these centers faster, or using these centers to guide and mentor primary care providers, would dramatically enhance quality of care for patients.

KEY STAKEHOLDERS IN THE EPILEPSY COMMUNITY

RESEARCH GRANTMAKING ORGANIZATIONS

Many nonprofit organizations specifically focus on charitable giving to support epilepsy. The majority of these organizations focus on improving awareness, providing patient support, and/or aiding research for cures. We identified national organizations with annual revenues greater than \$500,000 that provide direct current support for epilepsy research. Financial information for these organizations from fiscal year 2014, from the 990 tax form, is provided in the table below. Additional information regarding their mission, key research funding mechanisms, and clinical trials support activities is also provided below.

Table 5. Charitable Organizations Supporting Epilepsy Research with Annual Revenues Greater Than \$500,000

Organization	Revenue	Research Support	Research/Expense Ratio
CURE: Citizens United for Research in Epilepsy	5,390,158	4,832,430	90
Epilepsy Foundation of America	14,678,254	2,323,297	16
American Epilepsy Society	6,715,581	1,043,033	16
Pediatric Epilepsy Research Foundation	7,750,837	580,965	7
Dravet Syndrome Foundation	918,743	515,447	56
Tuberous Sclerosis Alliance	4,378,947	457,520	10
Child Neurology Foundation	1,106,428	255,163	23

CURE: CITIZENS UNITED FOR RESEARCH IN EPILEPSY

MISSION

The mission for CURE: Citizens United for Research in Epilepsy mission is to cure epilepsy, transforming and saving millions of lives. CURE identifies and funds cutting-edge research, challenging scientists worldwide to collaborate in pursuit of this goal. CURE's commitment is unrelenting. The majority (90 percent) of its fundraising goes directly toward this goal. Since its inception in 1998, the six hallmarks of every CURE program and grant have included (1) patient-centricity and direct patient-input into the project, (2) collaboration among patients, clinicians, and researchers both inside and outside the epilepsy field, (3) advancing research in understudied, underfunded areas (CURE has spearheaded research efforts in SUDEP, pediatric epilepsy, therapy-resistant epilepsy, traumatic brain injury, and many therapies that are now in clinical trials), (4) advancing treatments that target the underlying causes of epilepsy rather than just suppressing seizures, (5) training the next generation of researchers, and (6) raising awareness of how devastating epilepsy can be for many.

RESEARCH FUNDING MECHANISMS

CURE funds research grants ranging from \$50,000 to \$250,000 for 1 to 2 years to senior researchers, early-career investigators, and postdoctoral fellows. CURE also partners with the Howard Hughes Medical Institute to support

clinical research fellows. Additionally, CURE funds epilepsy research conferences that bring together many epilepsy stakeholder groups, especially patients, as well as young investigators to attend epilepsy seminars at academic and medical institutions around the globe. Furthermore, CURE actively supports three collaborative, team-driven, multimillion dollar initiatives: the Epilepsy Genetics Initiative (EGI) in collaboration with National Institute of Neurological Disorders and Stroke (NINDS), the Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy (TAPTE) Initiative in partnership with the Department of Defense (DOD), and the Infantile Spasms Initiative. Below is a summary of these initiatives. For more information about these awards and initiatives, please visit its website [here](#).

EPILEPSY GENETICS INITIATIVE IN PARTNERSHIP WITH NINDS (NIH)

EGI has created a centralized database to hold the genetic and clinical data of people with epilepsy and is the only public database of its kind. In addition to making the data available to investigators to advance epilepsy genetic research, EGI seeks to help patients to discover the genetic cause of their epilepsy. The data in EGI are analyzed every 6 months until a genetic cause of the person's epilepsy is found. Given the exponential rate of gene discovery that is occurring in epilepsy, repeat analysis of genetic data is crucial. Newly identified causes of epilepsy are then reported back to the patient's doctor, who can then inform the patient. This precision medicine-based initiative is also supported by NINDS and the John and Barbara Vogelstein Foundation.

TEAM APPROACH TO THE PREVENTION AND TREATMENT OF POST-TRAUMATIC EPILEPSY (TAPTE) INITIATIVE IN PARTNERSHIP WITH THE DOD

TAPTE's goal is to establish a multicenter, multi-investigator research team focused on post-traumatic epilepsy (PTE) that will rapidly translate patient-relevant findings at the molecular, cellular, and systems levels into novel therapies. The ultimate goal is to use this research to prevent the development of PTE from TBI. Based on previous successes within the epilepsy community, CURE was awarded a prestigious DOD grant to use its team science model to rapidly advance the most promising research in PTE. The model will build a "critical mass" of investigators with similar research interests and diverse backgrounds to address and execute PTE research via a team science approach. The investigative team will work closely with the CURE foundation, which will proactively monitor research progress and advise the consortium on the directions to take to ensure ultimate success. Key opinion leaders in both TBI and epilepsy research have been assembled to guide the development of a Request for Applications and their subsequent review. The opinion leaders will work closely with the consortium to ensure that TAPTE's goal will be reached, and the two groups will have continuous dialog mediated by CURE.

INFANTILE SPASMS INITIATIVE

CURE Formed this "dream team" to break down barriers and fight Infantile Spasms (IS), a severe epilepsy characterized by spasms that begin between 3-7 months of age and often leads to other seizures types as well as profoundly negative long-term developmental and cognitive consequences. Treatments are ineffective in more than 40 percent of IS infants; thus CURE spearheaded this first-ever research-by-consortia effort in the epilepsy space. This Team Science initiative funds cutting-edge research to understand the biology that underlies IS and to develop targeted therapies. The lead investigators bring a wealth of expertise and perspectives to a dream team that spans adult and pediatric neurology, basic mechanisms of the epilepsies, animal modeling, human genetics, and clinical trial design and execution. Patient input for the project has been included since day 1.

EPILEPSY FOUNDATION OF AMERICA (EF)

MISSION

The Epilepsy Foundation has a broad mission to lead the fight to overcome the challenges of living with epilepsy and to accelerate therapies to stop seizures, find cures, and save lives. The first part of the mission is achieved by providing caring help and support to people affected by seizures, as well as through education, advocacy and supportive care services both digitally and in communities across the country. The second part of the mission is in supporting research with an emphasis on driving innovative new therapy development and supporting strategic partnerships.

RESEARCH FUNDING MECHANISMS

The Epilepsy Foundation supports research initiatives through a number of targeted research support calls, the Epilepsy Therapy project, the SUDEP Institute, the Epilepsy Innovation Institute (EI2) and the RARE Epilepsy Network Patient Registry Initiative.

EPILEPSY THERAPY PROJECT

The mission of the Epilepsy Therapy Project (ETP) is to provide financial support, as well as scientific and business direction to promising new therapies. This is done by awarding New Therapies and Commercialization Grants which may support up to \$350,000 over two years; the program encourages 1:1 matching with company investment into the project. The Foundation's Shark Tank awards are made from a pool of \$200,000, with winners selected based on shark-tank judges and audience participation at a national Epilepsy Pipeline conference. The Foundation also offers the Epilepsy Innovation Seal of Excellence, a peer-reviewed endorsement award for spurring interest in future investors. More information is available [here](#).

SUDEP INSTITUTE

The Epilepsy Foundation's SUDEP Institute works to prevent Sudden Unexpected Death in Epilepsy (SUDEP) and support people confronting the fear and loss caused by SUDEP. The SUDEP Institute supports research through the SUDEP challenge initiative for discovering biomarkers and preventing SUDEP. The prize for a validated biomarker for SUDEP is 1 million dollars. More information is available [here](#).

EPILEPSY INNOVATION INSTITUTE

To develop a platform for driving continuous innovation in epilepsy research, the Epilepsy Foundation recently launched the Epilepsy Innovation Institute (EI2). EI2 focuses on identifying patient-centered challenges, encouraging radical new ideas, and incorporating novel expertise and technologies from other relevant fields of science to come up with novel solutions to those challenges.

AMERICAN EPILEPSY SOCIETY

MISSION

The American Epilepsy Society's (AES) mission is to promote research and education for professionals dedicated to the prevention, treatment, and cure of epilepsy. AES is the affiliate of the International League Against Epilepsy, whose mission aligns with AES on the international scale.

RESEARCH FUNDING MECHANISMS

AES funds investigator awards ranging from \$20,000 to \$50,000 for all levels of research training, from pre-doctoral fellows to junior investigator awards to seed grant money for established investigators. AES also partners with smaller epilepsy foundations to support targeted funding for research. For more information about these awards, please visit its website [here](#).

PEDIATRIC EPILEPSY RESEARCH FOUNDATION

The mission of the Pediatric Epilepsy Research Foundation is to support pediatric neurologists by providing educational information as well as clinical and basic science research grants related to epileptic conditions in pediatric populations.

RESEARCH FUNDING MECHANISM

The Foundation provides a 2-year award for up to \$200,000 to United States and Canadian neurologists performing clinical, translational, or basic science research pertaining to epilepsy in pediatric populations. This grant can be either a career development grant award or one for developing better infrastructure and or patient registries. To promote accountability, 10 percent of the award is withheld until the awardee submits a yearly interim scientific report. For more information about these awards, please visit its website [here](#).

DRAVET SYNDROME FOUNDATION

The Dravet Syndrome Foundation focuses on raising research funds for Dravet Syndrome, a rare severe form of epilepsy.

RESEARCH FUNDING MECHANISM

The Dravet Syndrome Foundation provides 1-year \$50,000 postdoctoral awards or 2-year \$100,000-\$160,000 awards for established investigators addressing basic science research questions about Dravet Syndrome. It also provides support for the Ion Channel Patient Registry and hosts a biennial research conference. For more information on the Dravet Syndrome Foundation, one can visit its website [here](#).

TUBEROUS SCLEROSIS ALLIANCE

The Tuberous Sclerosis Alliance is a patient advocacy foundation focused on improving current quality of care as well as research in the field for tuberous sclerosis.

RESEARCH FUNDING MECHANISMS

The Tuberous Sclerosis Alliance provides 2-year, \$75,000 postdoctoral fellowship and research grants as well as awards for \$100,000/year for 3 years that support innovative tuberous sclerosis research of an established investigator. More information about these awards can be found on its website [here](#).

CHILD NEUROLOGY FOUNDATION

The Child Neurology Foundation's (CNF's) overall mission is to improve the lives of children with neurological disorders through patient advocacy, education, and research funding. It supports research in pediatric epilepsy, especially the epileptic encephalopathies (a collection of rare syndromes where the seizures also contribute to further cognitive and behavioral delay in the child's development).

RESEARCH FUNDING MECHANISMS

CNF partners with industry and other foundations to provide \$30,000 to \$100,000 for a pediatric neurologist to conduct basic or clinical research. It also supports a summer clinical research scholarship for a first- or second-year U.S. or Canadian medical student interested in training as a child neurologist. For more information about the CNF awards, please visit its website [here](#).

COLLABORATIVE RESEARCH INITIATIVES

Several strategic partnerships have formed in the epilepsy research field. These partnerships are either consortia established between professional societies or foundations or through government-sponsored programs.

CONSORTIA

INTERNATIONAL LEAGUE AGAINST EPILEPSY

The International League Against Epilepsy (ILAE) is a consortia of professional epilepsy societies worldwide comprising more than 100 national chapters. The ILAE has three main goals:

- Advance and disseminate knowledge about epilepsy
- Promote research, education and training
- Improve services and care for patients, especially by prevention, diagnosis, and treatment

It achieves these goals by setting the clinical definitions and syndrome subtypes for epilepsy, promoting conferences, and publishing its findings in the journal ILAE journals *Epilepsia*, *Epilepsia Open*, and *Epileptic Disorders*. For more information about the ILAE, please visit its website [here](#).

THE TRANSLATIONAL TASKFORCE (AES IN PARTNERSHIP WITH ILAE)

This taskforce is charged with outlining a roadmap to optimize preclinical research. For more information about this taskforce, please visit its website [here](#).

EPILEPSY LEADERSHIP COUNCIL

The Epilepsy Leadership Council consists of more than 30 epilepsy professional organizations in the U.S., disease specific/patient advocacy organizations, and governmental agencies working to identify shared needs and develop collaborative projects designed to provide support within the community, shape policy, and stimulate research to improve the lives of those with epilepsy. For more information about the Epilepsy Leadership Council, please visit its website [here](#).

PEDIATRIC EPILEPSY RESEARCH CONSORTIA (PERC)

The Pediatric Epilepsy Research Consortia (PERC) is a nonprofit organization focused on assessing healthcare outcomes in pediatric epilepsy care by having multicenter collaborations between United States pediatric epilepsy centers. The overall mission is to provide a network and infrastructure to facilitate collaborative practice-changing research for the improvement of overall quality of care for children with epilepsy. For more information about this consortia, please visit its website [here](#).

EPILEPSY STUDY CONSORTIA

The Epilepsy Study Consortia is a group of renowned epilepsy scientific investigators from academic medical research centers whose mission is to accelerate and optimize clinical trial design and methodology. For more information about this consortia, please visit its website [here](#).

RARE EPILEPSY NETWORK

The Rare Epilepsy Network is a network of 26 small rare epilepsy foundations from the Epilepsy Leadership Council partnering with the Epilepsy Foundation to develop a registry. It is currently funded by a Patient Centered Research Outcomes Initiative (PCORI) grant. The purpose of the REN is to expedite research into the rare epilepsies. The initial goals of the network is to better understand how many different epilepsy subtypes there are, whether there are cluster areas of epilepsy subtypes that do not have clinics to address their unmet need, and what type of medications these different epilepsy syndromes are being prescribed. More information about the Rare Epilepsy Network can be found on its [website](#).

GOVERNMENT-SPONSORED PROGRAMS

AES/NINDS BENCHMARK STEWARDS OF EPILEPSY

Since 2000, the Epilepsy Program at the National Institute of Neurological Disorders and Stroke (NINDS) has convened renowned epilepsy experts (called benchmark stewards) to establish the priorities of the NINDS epilepsy research program. These stewards are selected by the American Epilepsy Society (AES). Following each meeting,

the program publishes a report that establishes a framework for epilepsy research, detailing key unmet needs and research areas in the field and benchmarking progress over the next 5 to 10 years to help advance epilepsy research. These benchmark stewards have highlighted the need to prevent epileptogenesis, address aspects of epilepsy beyond seizures, and confront the challenges of SUDEP. For more information about the benchmarks, please visit its website [here](#).

EPILEPSY CENTER WITHOUT WALLS INITIATIVE

These are NINDS supported consortia which tackle major hurdles to the advancement of epilepsy research and treatment through large, collaborative approaches. The first center without walls initiative, known as Epi4K, sequenced four thousand people living with epilepsy to understand the genetic underpinnings of epilepsy. The second center without walls initiative, focused on SUDEP (sudden unexpected death in epilepsy), to identify potential factors that could indicate that someone was at risk of SUDEP. The third, and most recent, center without walls initiative is to promote collaborative preclinical and clinical research to prepare for translational and clinical development of disease-modifying or prevention therapies for epilepsy. For more information, visit its website [here](#).

EPILEPSY THERAPY SCREENING PROGRAM

Known for four decades as the Anticonvulsant Screening Program (ASP) this program changed its name in 2016. The mission of the Epilepsy Therapy Screening Program (ETSP) is to encourage and facilitate the discovery of new therapeutic compounds that address unmet medical needs in epilepsy. Based on a strong foundation of well-established rodent anti-seizure assays, ETSP has recently refined its focus on pharmaco-resistant epilepsy and is rapidly expanding into areas of disease prevention and modification. The name change underscores the expanded focus beyond drugs that only symptomatically treat seizures. For more information about the program and the working report detailing its future directions, please visit its website [here](#).

INTERAGENCY COLLABORATIVE TO ADVANCE RESEARCH IN EPILEPSY (ICARE)

This program is led by NINDS and has identifies area for collaborations between research efforts of federal agencies and voluntary organizations for epilepsy. The ICARE organizations participate in a shared portfolio analysis of funded grants, which can be searched on its website [here](#).

CENTERS FOR DISEASE CONTROL AND PREVENTION

The Centers for Disease Control and Prevention (CDC) epilepsy program has four main areas of foci. Specifically, the program spearheads self-management research, program implementation, and dissemination; establishes and expands surveillance and data collection to describe the burden of epilepsy, evaluate prevention efforts, and prioritize program development; prevents known risk factors for epilepsy (e.g., cysticercosis infection, traumatic brain injury, stroke); and develops and promotes programs that create a more supportive environment for people with epilepsy.

CDC supports the Managing Epilepsy Well (MEW) Network, a group of eight CDC Prevention Research Centers collaborating as a community of practice to advance the science on epilepsy self-management by facilitating and

implementing research, conducting research in collaboration with stakeholders, and broadly disseminating research findings. For more information about the MEW Network and available evidence-based programs, please visit its website [here](#).

THE DEPARTMENT OF HEALTH AND HUMAN SERVICES INITIATIVE: HEALTHY PEOPLE 2020

Healthy People provides science-based, 10-year national objectives for improving the health of all Americans. The initiative is grounded in the principle that setting national objectives and monitoring progress can motivate action to improve population health. Healthy People integrates input from public health and prevention experts, a wide range of federal, state, and local government officials, a consortium of more than 2,000 organizations, and the public. In 2013, Healthy People established the first national objective for epilepsy to increase the proportion of people with epilepsy and uncontrolled seizures who receive appropriate medical care. Healthy People 2020 provides a forum to engage multiple societal sectors (e.g., healthcare, public health, business, education, transportation) to take action and contribute to reaching Healthy People targets.

DIFFERENT EPILEPSY TYPES FROM AN ILAE COMMISSIONED REPORT**EPILEPSY SYNDROMES**

Some types of epilepsies can be classified as syndromes that come at distinct ages and have a very clear clinical profile. Clinicians can use these classifications to infer the best course of treatment. Below is the list of syndromes broken down by age of onset. Not all epilepsies will fall under this list.

NEONATAL PERIOD

- Benign Familial Neonatal Epilepsy (BFNE)
- Early Myoclonic Encephalopathy (EME)
- Ohtahara Syndrome

INFANCY

- Epilepsy of infancy with migrating focal seizures
- West Syndrome
- Myoclonic Epilepsy in Infancy (MEI)
- Benign Infantile Epilepsy
- Benign Familial Infantile Epilepsy
- Dravet Syndrome
- Myoclonic Encephalopathy in non-progressive disorders
- Sturge-Weber
- Tuberous Sclerosis Complex

CHILDHOOD

- Febrile Seizures Plus (FS+) (can also start in infancy)
- Panayiotopoulos Syndrome
- Epilepsy with Myoclonic Atonic seizures
- Benign Epilepsy with Centrotemporal Spikes (BECTS)
- Autosomal-Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)
- Late Onset Childhood Occipital Epilepsy (Gastaut type)
- Epilepsy with Myoclonic Absences
- Lennox-Gastaut Syndrome (LGS)
- Epileptic Encephalopathy with Continuous Spike-and-Wave during Sleep (CSWS)
- Landau-Kleffner Syndrome (LKS)
- Childhood Absence Epilepsy (CAE)

ADOLESCENCE-ADULT

- Juvenile Absence Epilepsy (JAE)
- Juvenile Myoclonic Epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Progressive Myoclonus Epilepsies (PME)
- Autosomal Dominant Epilepsy with Auditory Features (ADEAF)
- Other familial temporal lobe Epilepsies

LESS SPECIFIC AGE RELATIONSHIP

- Familial Focal Epilepsy with Variable Foci (childhood to adult)
- Reflex Epilepsies
- Mesial Temporal Lobe Epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen Syndrome
- Gelastic Seizures with Hypothalamic Hamartoma
- Hemiconvulsion-Hemiplegia-Epilepsy

EPILEPSIES THAT DO NOT FIT SYNDROMES ABOVE

The epilepsies that do not fall under the syndromes listed above are classified on the basis of whether there is a structural or metabolic condition and whether the seizure is generalized or focal. Examples include but are not limited to:

- Malformations of cortical development
- Neurocutaneous Syndromes (such as tuberous sclerosis complex, Sturge-Weber Syndrome)
- Tumor
- Infection
- Trauma
- Angioma
- Perinatal insults
- Stroke

COMMON ANTI-SEIZURE MEDICATIONS SORTED BY SEIZURE TYPE

Common FDA-Approved Anti-Seizure Medications by Treatment of Seizure Type Observed

Primary Generalized Tonic–Clonic Seizures	Focal Seizures/ Secondary Generalized Seizures	Absence Seizures	Myoclonic and Atonic Seizures	Acute Repetitive Seizures deemed a medical emergency (seizures lasting >5 min)
First-line agents				
Lamotrigine Topiramate Valproic acid	Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Valproic Acid	Ethosuximide	Lamotrigine Valproic acid	Diazepam Midazolam
Alternative agents				
Carbamazepine Felbamate Levetiracetam† Oxcarbazepine Phenobarbital Phenytoin Primidone Zonisamide†	Bivaracetam† Eslicarbazepine Ezogabine† Felbamate Gabapentin Lacosamide Levetiracetam† Perampanel† Phenobarbital Pregabalin Primidone Rufinamide† Tiagabine† Topiramate Vigabatrin Zonisamide†	Clonazepam	Clonazepam Felbamate Levetiracetam†	

†Used as add-on therapy (in addition to another anti-seizure drug).

Not all of the anti-seizure medications listed in the table have been tested for safety in the pediatric population, such as children under the age of 2. In those cases, this table might not apply.

COMMON ANTI-SEIZURE MEDICATIONS SORTED BY MECHANISM OF ACTION

Common FDA-Approved Anti-Seizure Medications Sorted by Mechanism of Action

Targeting Neurotransmitters			Targeting Ion Channels	
Potentiating GABA Signaling	Reduce Glutamate Signaling	Blocking Neurotransmitter Release	Blocking Sodium Voltage Gated Channels	Blocking Calcium Channels
Carbamazepine* Clobazam Clonazepam Diazepam Felbamate* Gabapentin Midazolam Phenobarbital Primidone* Tiagabine Topirimate* Valproate* Vigabatrin	Felbamate* Perampanel Topiramate*	Brivaracetam Levetiracetam*	Carbamazepine* Eslicarbazepine Lacosamide Lamotrigine Oxcarbazepine Phenytoin Primidone* Rufinamide Topiramate* Valproate* Zonisamide*	Ethosuximide Levetiracetam* Pregabalin Topiramate* Zonisamide*

* Multiple mechanisms of action.

GLOSSARY

Absence Seizure	Absence seizures result in a person “spacing out” for up to 10-20 seconds. Unlike daydreaming, these seizures can occur during physical activity, and they cannot be interrupted. These seizures are most commonly seen in children ages 4-14.
Active Epilepsy	Active epilepsy is defined as adults who reported a history of epilepsy or seizure disorder and either were currently taking medication to control it, or had one or more seizures in the past year, or both.
Atonic Seizure	Atonic means without tone. In an atonic seizure, the muscles suddenly lose strength. These seizures are sometimes called drop attacks because the person seizing may suddenly drop something or fall to the ground. These seizures last less than 15 seconds, but depending on where the person falls, serious injury can occur.
Cannabidiol (CBD)	CBD is the non-psychoactive compound of cannabis.
Clinical Trials	Clinical trials are research studies with human subjects that evaluate the safety and efficacy of potential interventions, including drugs, medical devices, and dietary therapies.
Clonic Seizure	Clonic seizures are repeated rhythmic jerking movements of the arms and legs, sometimes on both sides of the body, which cannot be stopped by restraint. Pure clonic seizures are rare to observe, and often are seen with other seizure types..
Cytokine	Cytokines are inflammatory signaling molecules.
Deep Brain Stimulation	This surgical procedure is approved for the treatment of advanced Parkinson’s disease in patients, as well as for epilepsy in Europe, and is currently in clinical trials in the U.S.
Disconnection Surgery	In this type of surgery, the surgeon disrupts nerve pathways, interrupting the ability of neurons to communicate, without removing any brain tissue.
Electroencephalography (EEG)	An EEG is a diagnostic tool to measure electrical activity over the scalp.
Epileptic Encephalopathies	This term describes epilepsies in which the epilepsy activity itself is known to contribute to the cognitive and behavioral impairments observed.
Epileptogenesis	This is the process whereby a brain becomes susceptible to recurrent seizures.
Excitatory Neurons	These neurons excite other neurons in the network to which they are connected.
Fast Track Status	The Food and Drug Administration grants Fast Track status to expedite the review of drugs that fill an unmet medical need.
Focal Seizure	Focal seizures (also called partial seizures) are due to abnormal activity in just one part of the brain.
Gamma-amino butyric acid (GABA)	GABA is the primary inhibitory neurotransmitter in the brain.
Generalized Seizure	General seizures result from abnormal activity occurring on both sides of the brain.
Glutamate	This is the primary excitatory neurotransmitter in the brain.
Inhibitory Neuron	These neurons inhibit other neurons in the network to which they are connected.
Ion Channel	This conduit can shuttle specific ions in or out of the cell depending on the ion channel type.
Ions	Ions are electrically charged molecules.
Ketogenic Diet	A ketogenic diet is a high-fat, low-carbohydrate diet with restricted caloric intake.
Ketones	Ketones are a byproduct of fat and can be used as a fuel substitute in lieu of carbohydrates.

Metabolites	These are molecules that are byproducts of the various chemical reactions occurring in the body.
Myoclonic Seizure	Myoclonus movements are brief, shock-like jerks of a muscle or group of muscles that usually last 1-2 seconds. Many have experienced a myoclonus movement when having a hiccup or when falling asleep. In epilepsy, myoclonic seizures usually cause abnormal movements on both sides of the body at the same time.
Neuronal Gap Junctions	These are specialized connections between neurons that directly connect the inside of two cells together through a passageway.
Neurotransmitter	A neurotransmitter is a chemical released by neurons upon stimulation.
Orphan Drug Status	The Food and Drug Administration grants Orphan Drug status to give tax incentives, waived FDA fees, and protocol assistance to pharmaceuticals developing a drug for a small patient population as well as extended market exclusivity rights.
Precision Medicine	Precision medicine is the practice of tailoring treatment to the individual's specific symptoms and biological makeup.
Reflex Seizures	A reflex seizure is triggered by a specific external stimulus such as a flashing light or a specific sound.
Repurposed Drug	This refers to a drug that is already FDA-approved for one disease or condition, which may be repurposed for another disease or condition. Because safety trials have already been conducted, such a drug could go straight to Phase II, thereby reducing time and cost of the clinical trial.
Resection Surgery	In this surgery, the area of the brain that causes seizures is removed.
Responsive Neurostimulation (RNS) Device	The RNS device is a microcomputer embedded within the skull that monitors abnormal electrical events in the brain and stimulates the brain in response to deter seizures.
Secondary Generalized Seizures	These seizures occur when a focal seizure spreads from one part of the brain to both sides of the brain.
Seizure Trigger	Factors that can precipitate a seizure in an epilepsy patient
Serotonin	A neurotransmitter in the brain that important for mood regulation, eating, and sleep.
Somatic Mutation	A somatic mutation is a gene mutation that occurs in one organ of the body but not throughout the whole body.
Status Epilepticus	This is the name for a seizure lasting longer than 5 minutes and is deemed a serious medical emergency.
Tonic Seizure	In contrast to an atonic seizure, in a tonic seizure, the muscle increases in tone and the body or limbs make sudden stiffening gestures. These seizures are commonly observed during sleep and usually last less than 20 seconds.
Tonic-Clonic Seizure	This is the seizure type most often portrayed in movies. The person seizing will lose consciousness, the muscles stiffen (tonic aspect), and then jerking movements (clonic aspect) are observed. These seizures usually last 1-3 minutes and take much longer to recover from.
Transcranial Direct Current Stimulation (tDCS)	This noninvasive brain stimulation treatment uses constant low current delivered to the brain area of interest via electrodes on the scalp and is currently under clinical trials for epilepsy.
Trigeminal Nerve Stimulation (TNS)	A TNS device stimulates the trigeminal nerve, the nerve running from the brain to the face and is responsible for sensation in the face and motor functions such as chewing.
Vagus Nerve Stimulation	The VNS device is a chest implant that helps to short-circuit seizures by stimulating the vagus nerve.

REFERENCES

1. “2014 NINDS Benchmarks for Epilepsy Research,” n.d. <http://www.ninds.nih.gov/research/epilepsyweb/2014Bechmarks-Final-PDF.pdf>.
2. “About Epilepsy: The Basics.” Epilepsy Foundation. Accessed February 17, 2016. <http://www.epilepsy.com/learn/about-epilepsy-basics>.
3. William S. Appleton. “Third Psychoactive Drug Usage Guide.” *Diseases of the Nervous System* 37, no. 1 (January 1976): 39–51.
4. Baulac, Michel, Hanneke de Boer, Christian Elger, Mike Glynn, Reetta Kälviäinen, Ann Little, Janet Mifsud, Emilio Perucca, Asla Pitkänen, and Philippe Ryvlin. “Epilepsy Priorities in Europe: A Report of the ILAE-IBE Epilepsy Advocacy Europe Task Force.” *Epilepsia* 56, no. 11 (November 2015): 1687–95. doi:10.1111/epi.13201.
5. Begley, C. E., M. Famulari, J. F. Annegers, D. R. Lairson, T. F. Reynolds, S. Coan, S. Dubinsky, et al. “The Cost of Epilepsy in the United States: An Estimate from Population-Based Clinical and Survey Data.” *Epilepsia* 41, no. 3 (March 2000): 342–51.
6. Berg, Anne T., Samuel F. Berkovic, Martin J. Brodie, Jeffrey Buchhalter, J. Helen Cross, Walter van Emde Boas, Jerome Engel, et al. “Revised Terminology and Concepts for Organization of Seizures and Epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009.” *Epilepsia* 51, no. 4 (April 2010): 676–85. doi:10.1111/j.1528-1167.2010.02522.x.
7. Betjemann, John P., S. Andrew Josephson, Daniel H. Lowenstein, and James F. Burke. “Trends in Status Epilepticus-Related Hospitalizations and Mortality: Redefined in US Practice Over Time.” *JAMA Neurology* 72, no. 6 (June 2015): 650–55. doi:10.1001/jamaneurol.2015.0188.
8. Brazil, Rachel. “Food Science: Fat Chance.” *Nature* 511, no. 7508 (July 10, 2014): S14–15.
9. Brinkmann, Benjamin H., Joost Wagenaar, Drew Abbot, Phillip Adkins, Simone C. Bosshard, Min Chen, Quang M. Tieng, et al. “Crowdsourcing Reproducible Seizure Forecasting in Human and Canine Epilepsy.” *Brain* 139, no. 6 (June 2016): 1713–22. doi:10.1093/brain/aww045.
10. Centers for Disease Control and Prevention. Epilepsy in adults and access to care—United States, 2012. *MMWR* 2012; 61(45); 909-913.
11. Cully, Megan. “Drug Development: Illuminated Targets.” *Nature* 511, no. 7508 (July 10, 2014): S12–13.
12. Detyniecki, Kamil, and Lawrence Hirsch. “Marijuana Use in Epilepsy: The Myth and the Reality.” *Current Neurology and Neuroscience Reports* 15, no. 10 (October 2015): 65. doi:10.1007/s11910-015-0586-5.
13. de Vries, Evelien E., Bart van den Munchhof, Kees P.J. Braun, Annet van Royen-Kerkhof, Wilco de Jager, and Floor E. Jansen. “Inflammatory Mediators in Human Epilepsy: A Systematic Review and Meta-Analysis.” *Neuroscience & Biobehavioral Reviews* 63 (April 2016): 177–90. doi:10.1016/j.neubiorev.2016.02.007.
14. Dolgin, Elie. “Technology: Dressed to Detect.” *Nature* 511, no. 7508 (July 10, 2014): S16–17.
15. Eisenstein, Michael. “Neurobiology: Unrestrained Excitement.” *Nature* 511, no. 7508 (July 10, 2014): S4–6.
16. Engel, Jerome, Asla Pitkänen, Jeffrey A. Loeb, F. Edward Dudek, Edward H. Bertram, Andrew J. Cole, Solomon L. Moshé, et al. “Epilepsy Biomarkers.” *Epilepsia* 54 Suppl 4 (August 2013): 61–69. doi:10.1111/epi.12299.

17. "Epilepsy_rb.pdf." Accessed February 17, 2016.
http://iom.nationalacademies.org/~media/Files/Report%20Files/2012/Epilepsy/epilepsy_rb.pdf.
18. EpiPM Consortium. "A Roadmap for Precision Medicine in the Epilepsies." *The Lancet. Neurology* 14, no. 12 (December 2015): 1219–28. doi:10.1016/S1474-4422(15)00199-4.
19. "Examination of Clinical Trial Costs and Barriers for Drug Development." Accessed August 29, 2016.
<https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>.
20. Franco, Valentina, Jacqueline A. French, and Emilio Perucca. "Challenges in the Clinical Development of New Antiepileptic Drugs." *Pharmacological Research* 103 (January 2016): 95–104.
doi:10.1016/j.phrs.2015.11.007.
21. Friedman, Daniel, and Orrin Devinsky. "Cannabinoids in the Treatment of Epilepsy." *The New England Journal of Medicine* 374, no. 1 (January 7, 2016): 94–95. doi:10.1056/NEJMc1512758.
22. Galanopoulou, Aristeia S., Paul S. Buckmaster, Kevin J. Staley, Solomon L. Moshé, Emilio Perucca, Jerome Engel, Wolfgang Löscher, et al. "Identification of New Epilepsy Treatments: Issues in Preclinical Methodology." *Epilepsia* 53, no. 3 (March 2012): 571–82. doi:10.1111/j.1528-1167.2011.03391.x.
23. Galanopoulou, Aristeia S., and Solomon L. Moshé. "In Search of Epilepsy Biomarkers in the Immature Brain: Goals, Challenges and Strategies." *Biomarkers in Medicine* 5, no. 5 (October 2011): 615–28.
doi:10.2217/bmm.11.71.
24. Gravitz, Lauren. "Sociology: Shedding the Shame." *Nature* 511, no. 7508 (July 10, 2014): S10–11.
25. Grone, Brian P., and Scott C. Baraban. "Animal Models in Epilepsy Research: Legacies and New Directions." *Nature Neuroscience* 18, no. 3 (March 2015): 339–43. doi:10.1038/nn.3934.
26. Institute of Medicine (U.S.), and Mary Jane England, ed. *Epilepsy across the Spectrum: Promoting Health and Understanding*. Washington, D.C: National Academies Press, 2012.
27. Jehi, Lara, Daniel Friedman, Chad Carlson, Gregory Cascino, Sandra Dewar, Christian Elger, Jerome Engel, et al. "The Evolution of Epilepsy Surgery between 1991 and 2011 in Nine Major Epilepsy Centers across the United States, Germany, and Australia." *Epilepsia* 56, no. 10 (October 2015): 1526–33.
doi:10.1111/epi.13116.
28. Löscher, Wolfgang, Henrik Klitgaard, Roy E. Twyman, and Dieter Schmidt. "New Avenues for Anti-Epileptic Drug Discovery and Development." *Nature Reviews. Drug Discovery* 12, no. 10 (October 2013): 757–76.
doi:10.1038/nrd4126.
29. McTague, Amy, Katherine B. Howell, J. Helen Cross, Manju A. Kurian, and Ingrid E. Scheffer. "The Genetic Landscape of the Epileptic Encephalopathies of Infancy and Childhood." *The Lancet Neurology* 15, no. 3 (March 2016): 304–16. doi:10.1016/S1474-4422(15)00250-1.
30. Narain, Charvy. "Genetics: Complex Expressions." *Nature* 511, no. 7508 (July 10, 2014): S8–9.
31. "NINDS Anticonvulsant Screening Program Report—May 29, 2015," n.d.
http://www.ninds.nih.gov/research/asp/asp_working_group_report_052915.htm.
32. Paz, Jeanne T., and John R. Huguenard. "Microcircuits and Their Interactions in Epilepsy: Is the Focus out of Focus?" *Nature Neuroscience* 18, no. 3 (March 2015): 351–59. doi:10.1038/nn.3950.
33. Russ, S. A., K. Larson, and N. Halfon. "A National Profile of Childhood Epilepsy and Seizure Disorder." *PEDIATRICS* 129, no. 2 (February 1, 2012): 256–64. doi:10.1542/peds.2010-1371.

34. Schachter, Steven C., John Guttag, Steven J. Schiff, Donald L. Schomer, and Summit Contributors. "Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit." *Epilepsy & Behavior: E&B* 16, no. 1 (September 2009): 3–46.
35. Schmoldt, A., H. F. Benthe, and G. Haberland. "Digitoxin Metabolism by Rat Liver Microsomes." *Biochemical Pharmacology* 24, no. 17 (September 1, 1975): 1639–41.
36. Sixty-eighth World Health Assembly Agenda. "Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications." Item 13.5, WHA68.20 (May 26 2015). http://www.ibe-epilepsy.org/wp-content/uploads/2015/05/A68_R20-en.pdf.
37. Staley, Kevin. "Molecular Mechanisms of Epilepsy." *Nature Neuroscience* 18, no. 3 (March 2015): 367–72. doi:10.1038/nn.3947.
38. Strzelczyk, Adam, Jens Peter Reese, Richard Dodel, and Hajo M. Hamer. "Cost of Epilepsy: A Systematic Review." *Pharmacoeconomics* 26, no. 6 (2008): 463–76.
39. Varvel, Nicholas H., Jianxiong Jiang, and Raymond Dingleline. "Candidate Drug Targets for Prevention or Modification of Epilepsy." *Annual Review of Pharmacology and Toxicology* 55 (2015): 229–47. doi:10.1146/annurev-pharmtox-010814-124607.
40. Wiebe, Samuel. "Perspective: The Surgical Solution." *Nature* 511, no. 7508 (July 10, 2014): S7.
41. "WHO | Epilepsy." Accessed August 29, 2016. <http://www.who.int/mediacentre/factsheets/fs999/en/>.