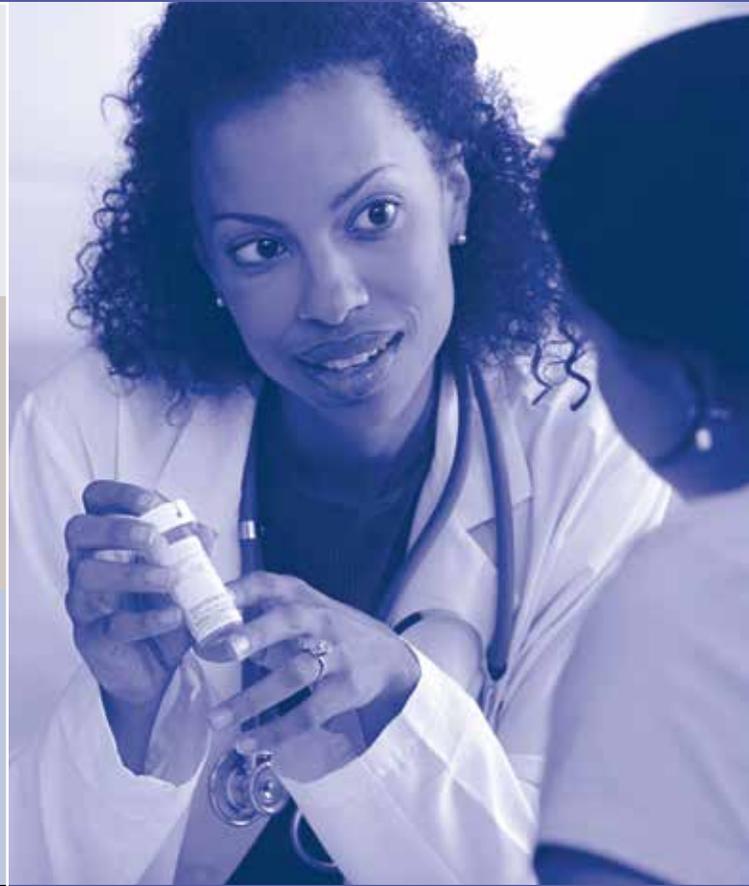




Curing the Epilepsies



The Promise of Research

National Institute of
Neurological Disorders
and Stroke

National Institutes of Health

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For individuals living with a treatment-resistant form of the seizure disorders known as “the epilepsies,” each day can bring debilitating seizures as well as challenges from co-occurring conditions that dramatically impair quality of life. This brochure, for people with the disorders, their caregivers, and advocates, outlines the state of progress made in the past decade toward achieving the Epilepsy Research Benchmarks, a set of widely recognized objectives aimed at prioritizing the efforts of scientists and health care providers to find cures for the epilepsies. Much of this work has been funded by grants from the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH).



Introduction

At least 2.3 million adults and nearly 500,000 children in the U.S. currently live with some form of epilepsy, a disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally, causing seizures. Each year, another 150,000 people are diagnosed with epilepsy. The disorders affect both males and females and can develop at any age. In the U.S. alone, the annual costs associated with the epilepsies are estimated to be \$15.5 billion in direct medical expenses and lost or reduced earnings and productivity.

The disturbances of neuronal activity that occur during seizures may cause strange sensations, emotions, and behaviors. They also sometimes cause convulsions, abnormal movements, and loss of consciousness. In some people, seizures happen only occasionally. Other people may

experience hundreds of seizures a day. There are many different forms of epilepsy, and symptoms vary greatly from one person to another. Recent adoption of the term “the epilepsies” underscores the diversity of types and causes.

About three-quarters of the individuals diagnosed with the epilepsies can control their seizures with medicine or surgery. However, about 25 to 30 percent will continue to experience seizures even with the best available treatment. Doctors call this treatment-resistant epilepsy. In some cases, people experience a type of seizure called status epilepticus, defined as seizures that last for more than five minutes or seizures that recur without recovery of consciousness. Prolonged status epilepticus can damage the brain and may be life-threatening.

1. About the Epilepsies

Seizures

Seizures can be classified as focal or generalized. Focal seizures begin in one area of the brain and may or may not spread to other areas. Generalized seizures are the result of abnormal neuronal (nerve cell) activity on both sides of the brain from the beginning of the seizure.

About 60 percent of people with epilepsy have focal seizures. Some focal seizures cause unusual sensations, feelings, or movements, but do not cause loss of consciousness. Other focal seizures cause a change in or loss of consciousness and may produce a dreamlike experience or strange, repetitive behavior. Focal seizures are often named for the area of the brain in which they originate. For example, temporal lobe epilepsy, or TLE, begins in the temporal lobe located on either side of the brain. TLE is the most common type of epilepsy to feature focal seizures and can sometimes be difficult to treat with available medications.

Generalized seizures impair consciousness and distort electrical activity of the whole or a large portion of the brain, leading to falls or abnormal movements. There are several different types of generalized seizures. In absence seizures, which usually begin in childhood or adolescence, an individual may appear to be staring into space or may have jerking or twitching muscles. Tonic seizures cause stiffening of muscles. Clonic seizures cause repeated jerking movements of muscles on both sides of the body. Myoclonic seizures cause jerks or twitches of the upper body, arms, or legs. Atonic seizures cause a loss of normal muscle tone, which may lead to falls or sudden drops of the head. Tonic-clonic seizures cause a combination of symptoms, including stiffening of the body and repeated jerks of the arms or legs as well as loss of consciousness.

Epilepsies with Childhood Onset

Compared to adults, infants and children have a relatively high risk of developing the epilepsies. Many epilepsy syndromes, such as infantile spasms, Lennox-Gastaut syndrome, and Rasmussen's encephalitis, begin in childhood. Infantile spasms usually begin before the age of six months and may cause a baby to bend forward and stiffen. Children with Lennox-Gastaut syndrome have severe epilepsy with several different types of seizures, including atonic seizures, which cause sudden falls called drop attacks. Rasmussen's encephalitis is a rare, chronic inflammatory neurological disease that usually affects only one hemisphere of the brain. It causes frequent and severe seizures and a loss of motor skills, and can lead to severe intellectual disability. Hypothalamic hamartomas can cause another rare form of epilepsy that presents during childhood and is associated

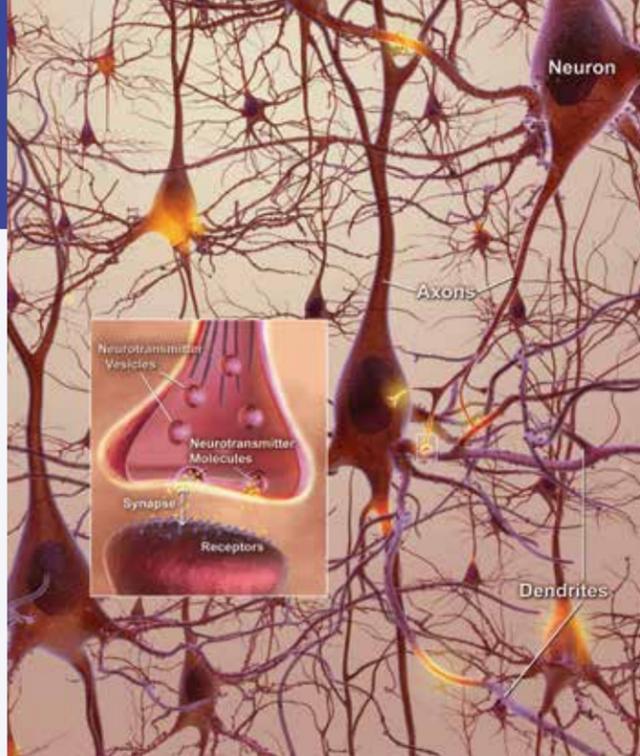


with malformations in the hypothalamus at the base of the brain. People with hypothalamic hamartomas have seizures that can resemble laughing (gelastic) or crying (dacrystic). Such seizures frequently go unrecognized or are difficult to diagnose.

Some childhood epilepsy syndromes, such as childhood absence epilepsy, may go into remission or stop entirely as a child matures, although this is not true in all cases. Other syndromes, such as juvenile myoclonic epilepsy and Lennox-Gastaut syndrome, are usually present for the rest of the person's life.

Children with delayed brain development and neurological disorders are more likely to have seizures. Seizures are more common, for example, among children with autism spectrum disorder, cerebral palsy, tuberous sclerosis complex (TSC), or Rett, Aicardi, or Down syndromes. In one study, one-third of children with autism spectrum disorder had treatment-resistant epilepsy.

The U.S. Federal government supports research to better understand the epilepsies and to reduce their burden through improved treatments and prevention. Much of this research support comes from the National Institutes of Health (NIH). The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH institute for research on the epilepsies. Several other NIH Institutes also fund epilepsy-related research. Representatives from NIH institutes, the Centers for Disease Control and Prevention (CDC), the Department of Defense, the Department of Veterans Affairs, and the U.S. Food and Drug Administration (FDA) work together as part of the Interagency Collaborative to Advance Research in Epilepsy (ICARE), which was formed to facilitate communication and opportunities for coordination among institutes and agencies sponsoring research related to the epilepsies.



Neurons communicate with each other by using signaling chemicals called neurotransmitters to send information across tiny spaces between neurons called synapses (see inset illustration). Neurotransmitters collect in sacs called vesicles. When the nerve receives a signal, these sacs release their neurotransmitters into the synapse. Receptors on the receiving neuron bind to the neurotransmitters, triggering a new electrical impulse, which in turn prompts neurotransmitters to be released into the synapse with the next neighboring neuron.

believe that some people with epilepsies have abnormally high levels of responsiveness to excitatory neurotransmitters, chemicals that increase the activity of nerve cells. Other people may have an abnormally low level of responsiveness to neurotransmitters that inhibit nerve cell activity. Either situation can result in too much neuronal activity and cause epilepsy. In some cases, inflammation and neuronal damage after a head injury, stroke, or other trauma may lead to epilepsy. In addition, the brain's attempts to repair itself after such injury may inadvertently generate abnormal nerve connections that lead to seizures. Supportive cells (known as glial cells) in the brain may play a role in certain types of epilepsy.

Causes

For about half of all people with an epilepsy, a cause for the disorder is not identified. In other cases, the epilepsies are clearly linked to genetic factors, infection, head trauma, stroke, brain tumors, or other identifiable problems.

The epilepsies have many possible causes. Almost anything that disturbs the normal pattern of brain circuit activity—from abnormal brain development to traumatic brain injury (TBI) or illness—can lead to seizures and epilepsy. For example, seizures may develop because of an abnormality in brain wiring that occurs during brain development, an imbalance of neuron-signaling chemicals called neurotransmitters, or a combination of these factors. Researchers

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2. Research Progress on the Epilepsies

In 2000, NINDS and epilepsy research and advocacy organizations co-sponsored a White House initiated conference, “Curing Epilepsy: Focus on the Future.” The conference has been viewed as a turning point for research on the epilepsies by shifting the focus from treating seizures to identifying cures, defined as “no seizures, no side effects, and the prevention of epilepsy in those at risk.” The first Epilepsy Research Benchmarks grew out of the momentum created by this conference, as a way to communicate and address important research priorities and as a framework for periodically “benchmarking” progress. A second conference in 2007, “Curing Epilepsy: Translating Discoveries into Therapies,” reassessed the state of research on the epilepsies and revised the Epilepsy Research Benchmarks, adding emphasis to the conditions that co-occur

with the epilepsies and sudden unexpected death in epilepsy (SUDEP). A third conference in 2013, “Curing the Epilepsies: Pathways Forward,” provided an update on the state of research and will result in another revision of the Benchmarks.

Today, more than a decade since they were first developed, the Benchmarks are increasingly embraced by the entire epilepsy community, including NIH, researchers, and professional and advocacy organizations. While the ultimate goal of curing the epilepsies has not yet been achieved, researchers have made substantial progress. Research on the epilepsies has yielded exciting advances across all areas of the Benchmarks.

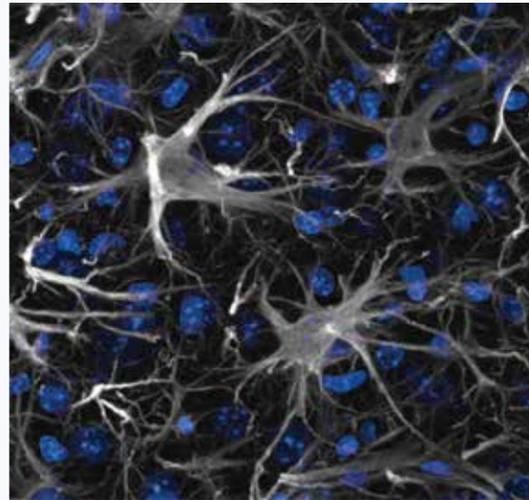


What New Discoveries Have Been Made About the Causes of the Epilepsies?

To understand how to prevent, treat, and cure the epilepsies, researchers first must learn how they develop. Where, how, when, and why do neurons begin to display the abnormal firing patterns that cause epileptic seizures? This process, known as epileptogenesis, is the key to understanding the epilepsies.

Researchers are learning more about the fundamental processes—known as mechanisms—that lead to epileptogenesis. The discovery of each new mechanism involved in epileptogenesis has the potential to yield new targets that can be affected by medications or other therapies to block that mechanism. Among this growing list of candidate mechanisms, two stand out as being closest to yielding potential targets for drug therapy: 1) the mTOR (mammalian target of rapamycin) signal transduction pathway; and 2) activation of the cytokine protein interleukin-1 β (IL-1 β).

- The mTOR pathway is a master regulator that is involved in several genetic and acquired forms of epilepsy. An inhibitor of the mTOR pathway is being studied for the prevention of seizures related to tuberous sclerosis complex (TSC), a rare genetic disease that causes the growth of noncancerous tumors in the brain and in other organs such as the kidney, heart, eyes, lungs, and skin.



The white, star-shaped cells in this photo are swollen astrocytes in brain tissue from a mouse model of epilepsy. This condition is called reactive gliosis. Astrocytes are the most common cells in the brain. Normally, they help the brain to function. However, they also produce the nerve-signaling chemical glutamate, which can trigger seizures. When reactive gliosis develops, astrocytes stop functioning correctly and may contribute to the development of epilepsy.

- In various types of epilepsy, inflammatory processes may play a key role. Cytokines are signaling molecules that, among other functions, help regulate the body's inflammatory responses. Researchers are exploring why IL-1 β appears to be activated in different types of epilepsy. An inhibitor of IL-1 β synthesis is being tested in people with treatment-resistant epilepsy.

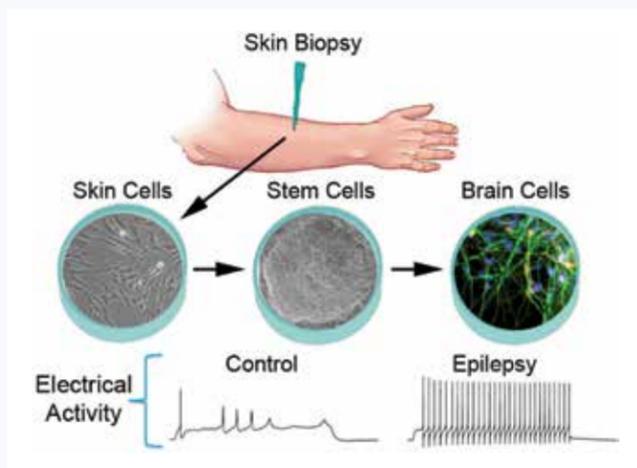
Other Areas of Epileptogenesis Research Include:

- Proteins in the cell membrane are crucial for generating the electrical impulses that neurons use to communicate with one another. For this reason, researchers are studying the membrane structure and the channels that allow molecules like sodium, calcium, and potassium to move across them to generate electrical impulses. A disruption in any of these processes can cause changes that may lead to epilepsy.
- Studies have suggested how a breakdown of the blood-brain barrier may lead to seizures. When proteins from the blood cross this important barrier between the circulatory system and fluid surrounding the brain, they trigger a reaction that leads to hyperactivity of neurons in the area of the brain surrounding the breakdown.
- Glial cells are non-neuronal cells that play a critical supportive role in the brain. For example, astrocytes are a type of glial cell that acts as a “housekeeper” by removing excessive levels of glutamate, a major neurotransmitter that mediates excitatory signals in the central nervous system. When astrocytes are impaired, levels of glutamate rise excessively in the spaces between brain cells, which may then

contribute to the onset of seizures. In animal studies, the introduction of ceftriaxone, an antibiotic that supports the housekeeping role of astrocytes, has been shown to reduce seizure frequency.

- The body's immune system may contribute to the development of certain forms of epilepsy. In aggressive forms of the disorders, antibodies may impair the function of brain receptors, leading to abnormal neuronal activity. Testing for many of these antibodies is already available, and findings from early-stage clinical trials suggest that strategies aimed at adjusting the body's immune system may provide a means of treating these otherwise untreatable forms of epilepsy.

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Researchers have taken skin cells from people with Dravet syndrome, turned them into stem cells, and then turned those stem cells into brain cells. Electrical activity among the brain cells can be measured, creating a testing ground for studying the disorder.

the fruit fly, zebrafish, and mouse that are now being used to test potential therapies for controlling seizures. In addition, researchers have successfully taken connective tissue cells from individuals with Dravet syndrome, reprogrammed them to create induced pluripotent stem cells (cells that can become any type of cell in the body), and differentiated them into neurons that also can be used to test potential drugs and to study the mechanisms that lead to Dravet syndrome.

Continued progress in the identification of genetic causes of the epilepsies could guide the care and medical management of individuals. In the case of heritable mutations, this will help affected families understand their risks.

A major driver of success on the genetics front is the advent of next-generation sequencing—high-throughput methods of genetic sequencing that have revolutionized the search for the genetic underpinnings of diseases and disorders. Next-generation sequencing has significantly cut the time and costs required to identify genes involved with the epilepsies, as well as other diseases.

Major collaborative efforts have enabled researchers to efficiently investigate the effects of many risk factors, including genetic ones, among large populations of people affected by the epilepsies.

Identify Biomarkers of Seizure Onset and Epileptogenesis

Researchers see a potential opportunity to prevent the epilepsies before the onset of recurrent spontaneous seizures. Surrogate measures of epileptogenic processes, or biomarkers, could aid in the development of interventions that would prevent epilepsy in at-risk individuals. Other types of biomarkers could help researchers and health care providers better identify and monitor seizure-onset zones or predict seizure occurrence, which could enable more targeted treatments. The identification of reliable biomarkers for the epilepsies is one of the more critical areas in need of research advances.



NINDS-sponsored programs aim to coordinate research efforts with the goal of accelerating advances in prevention, diagnosis, or treatment of the epilepsies and co-occurring conditions. For example, the **Epilepsy Centers without Walls** program brings together investigators from multiple disciplines, regardless of geographic location, and uses innovative approaches to address challenges identified by the Epilepsy Research Benchmarks. Among the first of such centers to be awarded funding, “Epi4K” aims to determine the genetic basis of human epilepsies in order to improve the well-being of individuals and family members living with these disorders. Epi4K investigators are working as a team in order to analyze the genomes of at least 4,000 people with well-characterized epilepsy. Among Epi4K’s first discoveries is the identification of *de novo* mutations involved in infantile spasms and Lennox-Gastaut syndrome. These epileptic encephalopathies are characterized as severe epilepsies that are typically resistant to medication and that involve developmental delay and cognitive and behavioral disabilities.

A number of changes in the brain shown on imaging and electroencephalography (EEG) are known to be associated with epilepsy-related processes. The challenge is that people without epilepsy also can have similar brain changes and there is little evidence to show clearly which of these changes is predictive of someone who will develop a form of epilepsy.

Newer technologies are allowing researchers to map epileptic networks and track seizure generation with increasing resolution. Implantable “microelectrodes” are revealing complex brain activity during seizures. Using microelectrodes, researchers are able to better characterize high-frequency oscillations (HFOs). Abnormal HFOs have been linked to seizure-onset zones and may serve as a biomarker of epileptogenesis; this could help identify people at risk for developing epilepsy after an initial insult to the brain, such as a stroke or TBI.

Investigators also have improved devices for measuring electrical activity in the brain. New electrode arrays are flexible enough to mold to the brain’s complex surface, providing unprecedented access for recording and stimulating brain activity. While these arrays have not yet been used in humans, they are a promising advance toward expanded options for epilepsy diagnosis and treatment.

Epilepsy researchers have increasingly explored how connections between different brain regions—structurally and functionally—may explain how seizures start in the first place. Much of this research grows out of observations that seizures are not merely the result of focal areas of hyperactivity, but arise from the complex interactions of the network. A better

understanding of how this network operates may explain, for example, why some people do not improve even after focal areas of hyperactivity, which appeared to be the source of seizure, are surgically removed.

Diffusion tensor imaging, a type of magnetic resonance imaging (MRI) that shows microstructural detail of tissues based on the diffusion of water molecules, has shown abnormal structural connectivity during focal and generalized seizures. Advances in MRI have shown that functional connectivity patterns in people with epilepsy differ from those of normal controls. Interestingly, patterns of abnormal functioning occur both during seizures and during the “resting-state” period between seizures.

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The zebrafish, a member of the minnow family, is making waves in genetic research. The fish can be bred to express mutations known to be associated with particular types of epilepsy, as well as other diseases.

Develop New Animal Models for Studying Epileptogenesis and for Testing Treatments

The diversity of epilepsy syndromes and their causes precludes investigators from using any single animal model system for learning about the epilepsies and for testing potential therapies. Multiple syndrome-specific models are therefore needed to advance research on the epilepsies.

Several substantial advances in the development of animal models have occurred over the last few years, including new models of Dravet syndrome, infantile spasms, cortical dysplasia, and viral encephalitis, as well as for stroke, TBI, and other conditions that can lead to acquired forms of epilepsy.

The zebrafish has emerged as a promising model for screening new drug compounds for antiseizure activity. Fish that are bred to express mutations known to be associated with particular types of epilepsy can be quickly and cost-effectively produced for research. The drosophila, or fruit fly, is another model developed to investigate the cellular mechanisms of the epilepsies.



Develop New Treatment Strategies and Optimize Existing Treatments

There have been several key advances in diagnostics, therapeutics, and technologies that are either approved or in various stages of approval in the U.S. and Europe.

New chemical entities have been developed for treatment-resistant epilepsy. For example, ezogabine (also called retigabine) was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the prevention of focal seizures by a novel mechanism of action. Several other potential drugs and chemical compounds (brivaracetam, perampanel, YKP3089, VX-765) are in development and also are aimed at preventing seizures by novel mechanisms.

In addition, several agents have been approved for specific seizure types or syndromes: rufinamide (Lennox-Gastaut syndrome), stiripentol (Dravet syndrome),

adrenocorticotrophic hormone also known as ACTH (infantile spasms), and vigabatrin (infantile spasms). mTOR inhibitors (such as everolimus) are being tested for the treatment of seizures and other manifestations of tuberous sclerosis complex (TSC). The drug everolimus has been approved by the FDA for preventing the growth of tumors in individuals with TSC.

Progress has been made in determining the best single-agent therapy for childhood absence epilepsy (CAE), the most common pediatric epilepsy syndrome, occurring in 10 to 17 percent of all children with epilepsy. People with CAE tend to have several seizures each day. In the interest of finding a drug regimen that would limit an individual's exposure to drug-related side effects, researchers compared ethosuximide, lamotrigine, and valproic acid to treat CAE. Ethosuximide was found to be the best single-agent therapy because of its optimal balance between effectiveness and relatively few side effects.



Paramedics stopped status epilepticus seizures earlier thanks to drug delivery with an autoinjector. Similar to the EpiPen used by people with serious allergic reactions, the autoinjector may someday be on hand for people with epilepsy and their families.

NINDS-funded researchers have made significant strides in improving the management of individuals with status epilepticus seizures. These prolonged seizures can be particularly challenging to treat given the difficulty of establishing an intravenous line (IV) when a person is having convulsions. The results of the randomized controlled trial, known as Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), showed that seizures stopped significantly earlier in people treated with midazolam delivered by an autoinjector compared to individuals treated with lorazepam by IV. The autoinjector is similar to the EpiPen drug delivery system used to treat serious drug reactions. Faster resolution of seizures also translated into fewer people requiring hospitalization.

Ongoing basic research efforts continue to identify targets for therapy development. For example, studies have focused on the role of gamma-aminobutyric acid (GABA), a key neurotransmitter that inhibits activity in the central nervous system. Other studies are investigating ways of blocking the activity of the excitatory neurotransmitter glutamate.

Given that the epilepsies involve so many different underlying mechanisms, the development of a single therapy is unlikely. Instead, management approaches will need to be tailored for specific syndromes.

In 1975, NINDS established the Anticonvulsant Screening Program (ASP) to promote the development and evaluation of new antiseizure drugs. At the time, few incentives existed for the pharmaceutical industry to support epilepsy research on the development of therapeutic agents. Since its launch, the ASP has been instrumental in bringing new antiseizure medications to the marketplace by giving researchers a common platform for submitting potential therapeutic agents to standardized testing in animal models. The resources provided to researchers through the ASP can save years in development time.

ASP's priorities have evolved to focus on the development of therapies aimed at preventing epileptogenesis, modifying the course of disease progression, finding therapies for the cases that do not respond to currently available treatments, and identifying specific epilepsy subtypes and their unmet needs. The ASP maintains a database of more than 30,000 submitted compounds, and plans are underway to improve the usefulness of the data for researchers pursuing novel compounds.

NINDS continues to look for new ways to improve the ASP. New assays and procedures are being developed and implemented to significantly expand the sensitivity of the traditional screening approach to identify novel pharmacotherapies targeting the major unmet medical needs in epilepsy.



Surgery

Surgery remains an effective option for individuals with treatment-resistant epilepsies. The most common type of surgery involves the removal of a seizure focus, the small area of the brain where seizures originate. In some extremely severe cases, surgeons perform a procedure called multiple subpial transection, which involves making cuts designed to prevent seizures from spreading into other parts of the brain while leaving the person's normal abilities intact. Doctors also may use surgical procedures called corpus callosotomy (severing of the nerve fibers that connect the two sides of the brain) or hemispherectomy (removal of half of the brain).

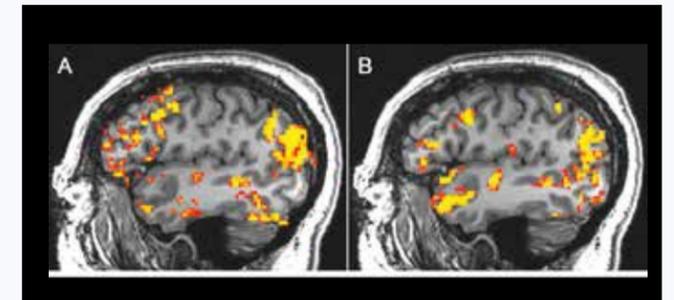
Researchers continue to refine surgical techniques to make them less invasive and to prevent cognitive and other neurological deficits that can result from surgery.

- New imaging technologies are key advances for localizing the effects of surgery and minimizing adverse events. Many epilepsy centers have begun to use functional magnetic resonance imaging (fMRI) to “map” language and memory zones prior to surgery. NIH-funded researchers are aiming to verify whether fMRI actually improves surgical outcomes and to standardize best practices for its use.
- Researchers also are looking for ways to combine imaging modalities to more accurately map language zones. In one study, for example, diffusion tensor imaging (DTI) is being used along with fMRI and magnetoencephalography (MEG), another brain mapping technique based on magnetic fields, to evaluate preoperative language processing and preserve key language zones during surgery for temporal lobe epilepsy.

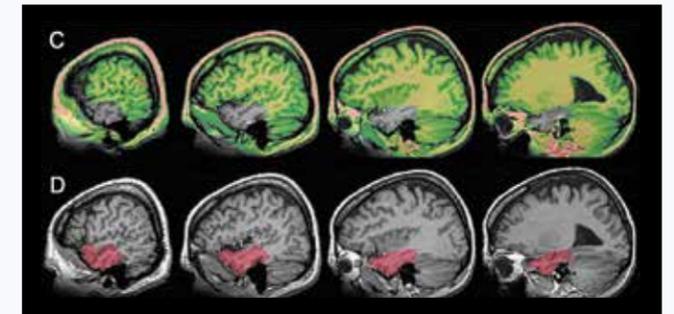
- Evidence suggests that high-frequency oscillations (HFOs) measured in the neocortex and temporal lobe may be biomarkers of epileptic networks, and can therefore help in surgical mapping and predicting outcomes after epilepsy surgery. Retrospective studies show that the removal of zones generating HFOs is associated with improved results following surgery.
- Minimally invasive MRI-guided laser surgery is being studied for the treatment of epilepsies associated with tumors, such as hypothalamic hamartomas and tuberous sclerosis complex. The technique involves drilling a very small hole in the skull through which a thermal laser is inserted to ablate an epileptogenic zone under MRI-guidance.

New imaging technologies are key advances

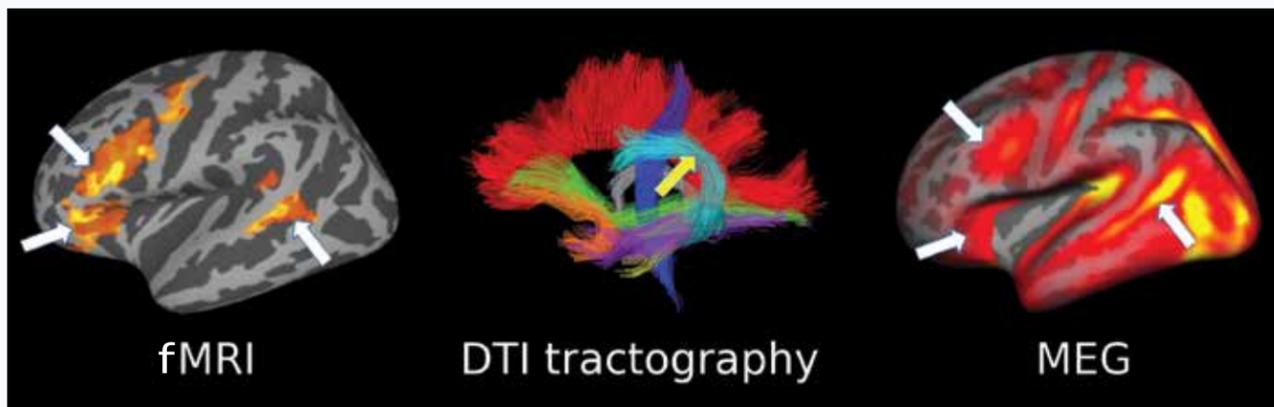
for localizing the effects of surgery and minimizing adverse events. Many epilepsy centers have begun to use functional magnetic resonance imaging to “map” language and memory zones prior to surgery.



Functional MRI (fMRI) provides a means for surgeons to more precisely target areas in the brain that, once removed, will control seizures, while also preserving language and memory function. Prior to surgery, fMRI results from a single patient (figures A and B) identify areas vital for language processing.



A structural MRI scan obtained after surgery (figure C) shows the anterior temporal lobe tissue removed (grey area). A 3D image of this surgically removed region (shown in pink in figure D) is digitally constructed.

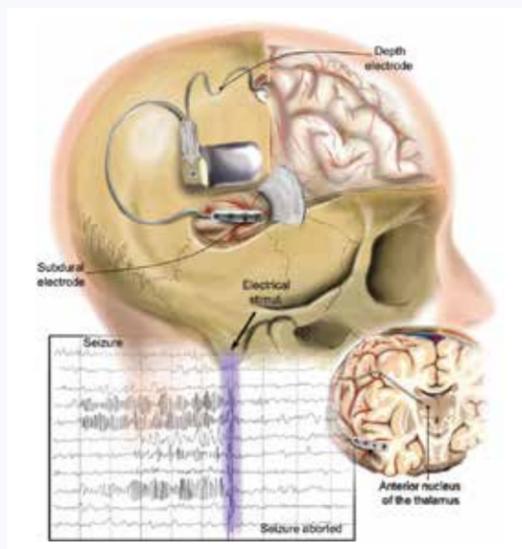


Brain Stimulation

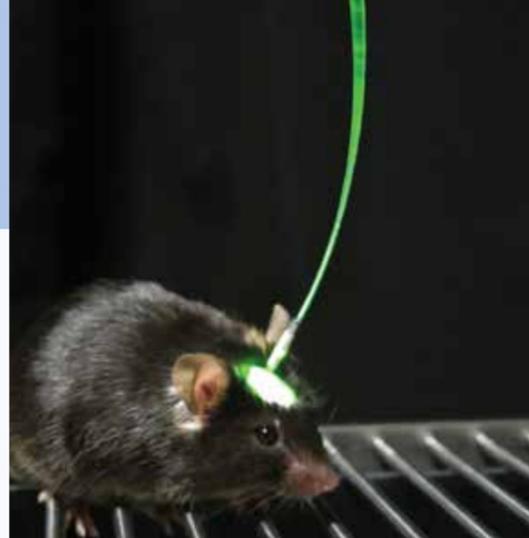
Electrical stimulation of the brain remains a therapeutic strategy of interest. The types of stimulation include: deep brain, intracranial cortical, peripheral nerve, vagal nerve, and trigeminal nerve. So far, deep brain stimulation has involved either the thalamus or the hippocampus, and only thalamic stimulation has been tested in a large clinical trial.

A clinical trial of deep brain stimulation in the anterior thalamic nucleus showed significant seizure reduction over the long term, and the majority of participants saw benefit. Thalamic stimulation has been cleared for use in Europe, but not in the U.S.

A report on trigeminal nerve stimulation showed efficacy rates similar to those for vagal nerve stimulation, with about half of the people responding (a responder is defined as having



A responsive or closed-loop stimulation system involves the implantation of electrodes on or adjacent to the area of the brain where seizures begin. The electrodes are attached to a neurostimulator implanted in the skull. With the detection of abnormal electrical activity, the neurostimulator sends a signal that disrupts that activity to prevent the seizure. Photo credit: Neurosurgical Focus, 2012.



Optogenetics delivers light-sensitive proteins to targeted brain cells. Once in place, the proteins can be inhibited or stimulated by exposure to light transmitted via fiber optics. Animal studies suggest that such an approach provides an exquisitely sensitive and highly targeted way of regulating of brain activity.

greater than a 50 percent reduction in seizure frequency). Freedom from seizures, although reported, remains rare for both methods.

NINDS-supported investigators are developing methods to predict seizures by analyzing brain activity patterns that precede their onset. A promising application of this research is the development of implantable devices that can detect a forthcoming seizure. Once detected, the implanted device administers an intervention, such as electrical stimulation or a fast-acting drug to prevent the seizure from occurring. The first generation of seizure control devices in clinical trials uses such seizure prediction technology. The NeuroPace RNS system is among these devices, known as responsive stimulation or closed-loop devices.

Optogenetics is an emerging experimental technique that may eventually lead to future generations of closed-loop devices. It involves the genetic delivery of light-sensitive proteins to specific populations of brain cells. The light-sensitive proteins can be inhibited or stimulated by exposure to light delivered by fiber optics. Although optogenetic methods are not currently used in humans, such an approach could allow highly targeted regulation of network excitability, providing a means for intervening at or before the onset of a seizure.

Researchers are trying to learn exactly how the ketogenic diet prevents seizures.

They hope to find ways to mimic its seizure-blocking effects without the dietary restrictions. Studies have advanced the understanding of the connection between energy metabolism and neuronal excitability.

Diet

A high-fat, very low carbohydrate ketogenic diet is an age-old treatment for medication-resistant epilepsies and there has been a renewed interest in recent years in how it works. The diet effectively reduces seizures for some people, especially children with certain forms of epilepsy. Studies have shown that more than 50 percent of people who try the ketogenic diet have a greater than 50 percent improvement in seizure control and 10 percent experience seizure freedom. However, for some people, the regimen is difficult to maintain.

Researchers are trying to learn exactly how the ketogenic diet prevents seizures. They hope to find ways to mimic its seizure-blocking effects without the dietary restrictions. Studies have advanced the understanding of the connection between energy metabolism and neuronal excitability, and in the process and may contribute to a better understanding of how the ketogenic diet promotes seizure control.

In addition, researchers are looking at modified versions of and alternatives to the ketogenic diet. For example, studies show promising results for a modified Atkins diet and for a low-glycemic-index diet, both of which are less restrictive and easier to follow than the ketogenic diet. However, well-controlled randomized controlled trials have yet to assess the approaches, and many questions remain about the optimal circumstances of their use.





Gene and Cell Therapies

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

Several proteins have been targeted for transfection. Animal studies have shown that it is possible to introduce a new protein into a cell, and in some cases, there has been an associated reduction in the frequency, duration, and severity of seizures.

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

Gene and cell therapies remain attractive and promising strategies for treating, and potentially curing, some forms of epilepsy. However, their advancement as a viable treatment option in people will require new technologies and methods that can target specific neurons in the brain. These approaches need to be able to create more long-lasting changes.

Viruses are introduced into brain cells,
which then act as “factories” to produce
potentially therapeutic proteins.

Preventing the Development of the Epilepsies

Until recently, therapy development for the epilepsies focused largely on treating seizures in people already affected by the disorders. Now, in addition to efforts to develop new and improved antiseizure treatments, researchers are striving to prevent the epilepsies among people at risk.

Measures that reduce the risk of head injury and trauma—such as improvements in automobile safety and the use of seat belts and bicycle helmets—can prevent epilepsies related to TBI. Good prenatal care, including treatment of high blood pressure and infections during pregnancy, can prevent brain damage in developing babies that may lead to epilepsy and other neurological problems later in life. Treating cardiovascular disease, high blood pressure, infections, and other disorders that affect the brain during adulthood and aging also may prevent some types of epilepsy.

However, while such measures can prevent brain damage from occurring in the first place, there are currently no interventions known to specifically reduce the risk of seizure onset once damage to the brain has occurred. None of the available antiseizure medications have been shown to modify the development of the epilepsies in people. Researchers are working to change this.

- Recent animal studies have helped clarify the mechanisms of hypoxic-ischemic encephalopathy (HIE) seizures (caused by a lack of oxygen in the brain), and clinical studies involving newborns have begun to assess potential treatment strategies. These include drugs both alone and in combination with each other or in combination with a strategy that involves deliberately cooling babies with HIE for the prevention of epilepsy.
- Adenosine is an inhibitory neuromodulator that is believed to promote sleep and suppress arousal. Studies in animal models have shown that increasing adenosine levels in the brain can inhibit the development of spontaneous recurrent seizures after an initial injury.



3. Reducing the Risk of Conditions that Co-occur with the Epilepsies



Psychiatric, Neurodevelopmental, and Sleep Disorders

Co-occurring psychiatric conditions are relatively common in individuals with epilepsy. In adults, depression and anxiety disorders are the two most frequent psychiatric diagnoses. Attention Deficit Hyperactivity Disorder and anxiety frequently affect children with epilepsy.

Therapies commonly used to treat depression in the general population have been shown in randomized controlled trials to be effective in treating depression in people with epilepsy. In those trials, depression medications did not appear to be associated with an increased risk of seizures. However, larger trials with longer followup would be required to provide reliable estimates of seizure exacerbation risk.

Basic research investigations currently are exploring the possibility that the development of depression, anxiety, and seizures may involve similar causes. In addition, studies of antiseizure drugs have focused on determining whether there may be an increased risk of suicide associated with specific medications.

People with neurodevelopmental disabilities, such as autism spectrum disorder, attention deficit disorder, and learning disabilities are known to be at higher risk for epilepsy. Further investigation is needed to better understand these associations and if there is a shared mechanism between these neurodevelopmental disabilities and the epilepsies.

Sleep disorders are common among people with the epilepsies. By one estimate, fully 70 percent of people with epilepsy had some form of disordered breathing during sleep. In another study, researchers found that certain types of seizures were associated with sleeping, while others were more common during times of wakefulness—suggesting that more research is needed on how these patterns might inform medication adjustment.

Sudden Unexpected Death in Epilepsy (SUDEP)

Some people with epilepsy are at risk of SUDEP, which for years was largely unrecognized. Estimates of SUDEP risk vary, but some studies suggest that each year approximately one case of SUDEP occurs for every 1,000 people with the epilepsies. For some, this risk can be higher, depending on several factors. People with more difficult-to-control seizures tend to have a higher incidence of SUDEP.

One study suggested that use of more than two antiseizure drugs at one time is a risk factor for SUDEP. However, it is not clear whether the use of multiple drugs causes SUDEP, or whether people who use multiple antiseizure drugs have a greater risk of death because their epilepsy is more severe or more difficult to control. People with tonic-clonic seizures, uncontrolled seizures, or epilepsy combined with other neurological disorders also have an elevated risk for SUDEP.

Findings from an analysis of four studies showed that the highest risk of SUDEP can be seen in men younger than 60 years of age with at least a 15-year history of epilepsy from unexplained causes, who had frequent generalized tonic-clonic seizures, and who were taking multiple antiseizure drugs. Although SUDEP is considered rare in children, some evidence suggests that children with certain types of epilepsies, such as Dravet syndrome, may have an elevated risk for SUDEP.

Seizures are known to alter breathing and cardiac activity. Research suggests that drug therapies that address respiratory arrest and implantation of cardiac devices may reduce the risk of SUDEP in some individuals.

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

NINDS, nonprofit lay and professional organizations, and the CDC are providing significant funding toward studies aimed at better understanding SUDEP risk factors and mechanisms, which may yield strategies for screening and prevention. Plans are underway for an **Epilepsy Center without Walls** initiative devoted to multi-disciplinary research on SUDEP and increased surveillance and epidemiology studies.

Progress in Managing Specific Populations

Pregnancy and the Epilepsies

Understanding how to treat epilepsy in pregnant women and the impact of antiseizure medications on an unborn child are of paramount importance and have been the focus of several studies. The American Academy of Neurology and the American Epilepsy Society conducted evidence-based systematic reviews of pregnancy-related studies among women with epilepsy.

Emerging data from the NINDS-funded Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study, as well as multiple hospital- and population-based registries, are helping to better characterize the risk of birth defects associated with antiseizure medications. In general, higher doses of these medications are associated with an increased risk of major congenital malformations. Findings from the registries and other studies include:

- Valproate is consistently associated with an increased risk of major congenital malformations, and studies suggest a specific increased risk of neural tube defects, such as spina bifida. Prenatal exposure to valproate has been shown to be associated with symptoms of autism in humans and animals. Valproate exposure in utero also has been shown to adversely affect a child's cognitive function, particularly verbal abilities.

- Carbamazepine may increase the risk of neural tube defects, but this is not a consistent finding. Verbal cognitive skills also have been shown to be impaired among children who were exposed to carbamazepine during gestation.
- Topiramate increases the risk of oral clefts (birth defects in which the tissues of the lip or mouth do not form correctly during fetal development) as demonstrated in multiple studies. The FDA has classified it as a category D drug in pregnancy, meaning that evidence shows that the drug involves risk to a developing fetus, but the potential benefits from the drug may warrant its use in pregnant women despite potential risks.
- Levetiracetam appears to have a lower risk of major congenital malformations than other antiseizure drugs.



- Motor, adaptive, and emotional behavioral functioning were impaired in children of mothers who had taken phenytoin, lamotrigine, valproate, or carbamazepine during pregnancy, with dose-response effects seen with valproate and carbamazepine. Breastfeeding did not affect cognitive health of the studied children.

Infants and Children

Febrile seizures occur in infants and young children and involve convulsions brought on by high fever. The vast majority of febrile seizures are brief and harmless. In rare cases, however, some children—including those with cerebral palsy, delayed development, or other neurological abnormalities—have an increased risk of developing epilepsy.

Results from an ongoing NINDS-funded study suggested that MRI and EEG may help determine which children with febrile seizures are subsequently at increased risk of developing epilepsy.

Older Adults

Epidemiological studies demonstrate that the elderly are at a substantially higher risk for the development of the epilepsies. In addition to stroke (hemorrhagic and ischemic), seizures in the elderly may be associated with brain tumors, TBI, and Alzheimer's disease.

NIH-funded researchers have found that blood concentrations of antiseizure medications fluctuate markedly among many residents of nursing homes even when there is no change in dosage and no change in other medications the



resident may be taking. Prospective studies will continue to follow older adults in nursing homes to help determine optimal levels of antiseizure drugs and to identify factors that may contribute to such fluctuations in drug levels.

Diagnosing, Treating, and Preventing Non-epileptic Seizures

An estimated five to 20 percent of people diagnosed with epilepsy actually have non-epileptic seizures (NES) which outwardly resemble epileptic seizures but are not associated with seizure-like electrical discharges in the brain. A history of traumatic events is among the known risk factors for psychogenic non-epileptic seizures, which are largely thought to be psychological in origin.

A NINDS-funded pilot trial showed a reduction in NES frequency when individuals with psychogenic non-epileptic seizures were treated with sertraline compared with a placebo. Two other studies showed a reduction in seizures and fewer comorbid symptoms following treatment with cognitive behavioral therapy.

4. Furthering Research on the Epilepsies



There are several ways in which individuals with epilepsy and their families can help move research forward. Resources include:

- People with epilepsy can help researchers test new medications, surgical techniques, and other treatments by enrolling in clinical studies. Information about finding and participating in clinical studies can be found at the NIH Clinical Trials and You website (www.nih.gov/health/clinicaltrials). Additional studies can be found at www.clinicaltrials.gov and through many pharmaceutical and biotech companies, universities, and other organizations. A person who wishes to participate in a clinical trial must ask his or her physician to work with the doctor in charge of the trial and to forward all necessary medical records.
- To learn more about why clinical trial research is important, visit the Human Epilepsy Research Opportunities (HERO) website at www.epilepsyhero.org.

- Pregnant women with epilepsy who are taking antiseizure drugs can help researchers learn how these drugs affect unborn children by participating in the Antiepileptic Drug Pregnancy Registry. This registry is maintained by the Genetics and Teratology Unit of Massachusetts General Hospital. For more information, call 1-888-233-2334 or visit the website at www.massgeneral.org/aed.
- People with epilepsies can help further research by making arrangements to donate tissue either at the time of surgery for epilepsy or at the time of death. Researchers utilize the tissue to study epilepsy and other disorders so they can better understand what causes seizures. Some brain banks accept tissue from individuals with epilepsy. Each brain bank may have different protocols for registering a potential donor. Individuals are strongly encouraged to contact a brain bank directly to learn what needs to be done ahead of the time of tissue donation. These banks include:

NICHD Brain and Tissue Bank for Developmental Disorders

University of Maryland School of Medicine
Department of Pediatrics
655 West Baltimore Street, 13-013 BRB
Baltimore, MD 21201-1559
800-847-1539
www.btbank.org

University of Miami Brain Endowment Bank

University of Miami Department of Neurology
1951 NW 7th Avenue, Suite 240
Miami, FL 33136
305-243-6219 or 800-862-7246
www.brainbank.med.miami.edu

National Disease Research Interchange/ National Human Tissue Resource Center

8 Penn Center, 15th Floor
1628 JFK Boulevard
Philadelphia, PA 19103
215-557-7361 or 800-222-6374
www.ndriresource.org

The Human Brain and Spinal Fluid Resource Center

11301 Wilshire Boulevard (127A)
Building 212, Room 16
Los Angeles, CA 90073
310-268-3536
www.brainbank.ucla.edu

Conclusion

The pace of research on the epilepsies has accelerated considerably over the past few decades. Progress has been made in understanding how and why the epilepsies develop and how they might be prevented. Investigators have identified a variety of potential new treatments, and they may soon be able to use knowledge about genetic variations and other individual differences to tailor treatment for each person. With time and continued work, the missing pieces of the puzzle will be filled in to form a complete picture of how to treat and prevent all types of epilepsy.

PHOTO CREDITS

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