Update to NINDS Epilepsy Research Benchmarks

Introduction

In March 2007, more than 400 epilepsy researchers, physicians, patients, family members, and voluntary health organization leaders participated in a two-day conference on the NIH campus. Organized by the NINDS in collaboration with epilepsy research and voluntary organizations, the meeting was a follow-up to an earlier conference held in March 2000 that established the first set of Epilepsy Research Benchmarks to guide future research directions.

Since the meeting in 2000, these Benchmarks have acted as both a spur and a guide for specific research areas. Substantial progress has been made. As a result, the 2007 conference's task was to evaluate the original Benchmarks and discuss new research directions. Participants voted on the most promising areas of research, as well as those that had been neglected but offered promise. Via the internet and voluntary organizations, the NINDS asked for public comment. The Epilepsy Benchmark Stewards gathered in October 2007 to discuss the comments received and to finalize the document.

Like the 2000 Benchmarks, the 2007 Benchmarks are not meant to include all areas of epilepsy research, but rather they represent significant research milestones that have to be achieved in order to find a cure for epilepsy—which is defined as the prevention of epilepsy in people at risk, and effective and safe therapy for those with the disorder. The Benchmarks propose research directions that will result in better understanding of the causes of epilepsy, more advances in technology to study these causes, and increased long-term collaboration among scientists, industry, and patient groups. Their implementation is the shared responsibility of the entire epilepsy community, including the NIH and its researchers, NIH grantees, epilepsy professional organizations, and the epilepsy patient community.

The Benchmarks have been written in lay language so that they can be widely shared. The NINDS looks forward to working with the epilepsy research community to achieve these Benchmarks in the coming years.

Area I *Prevent epilepsy and its progression*

A. Find unrecognized causes of epilepsy.

Background: Epilepsy has many causes. It may be the result of developmental problems due to genetic mutations that interfere with the normal "wiring" of the brain. It can also be caused by infection, tumors, stroke, or any kind of injury to the brain. In some cases, there is no obvious cause. Knowing more about how epilepsy develops will increase opportunities for new treatments.

B. Identify the biological mechanisms that turn a normal brain into an epileptic brain.

Background: A better understanding of where, how, when, and why neurons begin to display the abnormal firing patterns that cause epileptic seizures (the process known as epileptogenesis) will help researchers answer fundamental questions about how epilepsy develops and persists as a chronic disease.

Short Term

1. Find at least one genetic mutation or any other risk factor that makes an individual vulnerable to the development of epilepsy. Show how it changes the activity of networks in the brain.
2. Discover at least one mechanism that contributes to the development of epilepsy and is either reversible or has an influence on the brain during critical periods of early development.
3. Identify at least one specific role for mechanisms outside the brain (immune system cells, for example) in the development of epilepsy.
4. Identify at least one mechanism involving the behavior of networks of neurons that contributes to the development of epilepsy.

Long Term

5. Look for biological mechanisms in the brain that cause epilepsy and are common across different types of human epilepsy and animal models.
6. Identify changes in neurons at the cellular or molecular level that are associated with abnormalities in brain function.
7. Identify mechanisms native to the brain that stabilize brain function and therefore prevent "microsynchrony," an important step in seizure development.

C. Discover biomarkers that can predict the development of epilepsy.

Background: Biomarkers are biological markers—changes in cells, tissues, or organs—that are associated with the development of a disease. Biomarkers for epileptogenesis could be used to identify people who are at higher than average risk of developing epilepsy.

Short Term

1. Discover and test a biomarker to predict worsening or hard-to-treat epilepsy in people who have just begun to have seizures.
2. Discover and test a biomarker to predict the development of epilepsy in individuals who are known to be at high risk for the disease. Show it in animal models or people.

D. Identify ways to prevent epilepsy or stop it once it begins.

Background: Antiepileptic drugs are currently used to control the seizures of people with epilepsy. But not everyone responds well to the drugs and they can have bothersome side effects. A better approach would be to develop treatments that could prevent epilepsy from developing in the first place, or that could stop the disease once it begins.

Short Term

1. Identify at least one stabilizing process native to the brain that protects against the development of epilepsy or stops it from getting worse.

Long Term

2. Identify new treatments or therapies to prevent, interrupt, or reverse the development of epilepsy.

E. Develop new animal models for studying how epilepsy develops in the brain.

Background: Animal models are important tools for researchers. Models can help to answer questions about how epilepsy develops, how repeated seizures affect brain structure and function, and how epilepsy develops in people, depending upon their age.

Short Term

1. Develop at least one new animal model to understand how epilepsy develops and progresses.
2. Develop at least one new animal model of the epileptic encephalopathies of infancy and childhood—diseases that can lead to seizures.
3. Develop at least one new animal model that demonstrates the unique aspects of how epilepsy develops in the aging brain.

F. Test the effectiveness of prevention strategies.

Background: New therapies to prevent epilepsy must prove their effectiveness in clinical trials before they can be used in real life practice.

Short Term

1. Test the effectiveness of the prevention strategies in animal models of the disease and in people with epilepsy.

Area II *Develop new treatment strategies and improve current approaches in order to cure epilepsy*

A. Discover and describe the biological mechanisms in the brain that cause seizures.

Background: Understanding how seizures begin and end in the brain gives researchers opportunities to develop drugs or other treatments that can act before seizures begin, or stop them as soon as they start.

1. Define mechanisms that start, continue, and end seizures in the epileptic brain and which can be used as targets for treatment.
2. Use biosensors, imaging (brain scans), or other methods to define the networks in the brain that are responsible for producing seizures.

B. Develop new tools to help discover and test potential cures.

Background: Research tools such as markers, animal models, and screening techniques could predict if epilepsy will worsen, allowing doctors to better identify people who will benefit from aggressive therapies or surgery. These tools may also help in the discovery of new therapies.

1. Develop and test biological and other markers that pinpoint the locations of brain networks associated with the development of epilepsy.
2. Identify new molecules that could be developed into new drugs or treatments.

3. Develop methods (using screening strategies, biological markers, or surrogate markers) to determine which patients will respond well, or respond poorly, or develop bothersome side effects, to specific therapies.

C. Improve current treatments and develop new therapies and technologies.

Background: Individuals with recurrent seizures that are not controlled by current medications or surgery make up approximately 25 percent of the epilepsy patient population. Even when seizures are controlled, the quality of life for some people can be severely affected by the long-and short-term side effects of drugs or surgery.

1. Identify the factors and practices that are associated with the best outcomes of brain surgery for epilepsy.
2. Develop new approaches for targeted therapies using, for example, gene therapy, brain electrical stimulation, or drug therapy.
3. Develop cheaper and faster methods to screen drugs for specific types of epilepsy.
4. Start clinical trials to test new therapies, modify current treatments, and evaluate the success of treatment regimens that combine more than one therapy.

Area III *Prevent, reduce, or cure the diseases associated with epilepsy*

A. Identify other medical conditions that are associated with epilepsy. For each condition, describe the range of symptoms and the usual age of onset.

Background: Epilepsy is often associated with other disorders such as autism, Rett syndrome, cerebral palsy, and tuberous sclerosis. People with epilepsy also have a higher chance of developing many chronic disorders, such as ulcers, migraines, chronic fatigue, and bowel disorders. In many of these cases, the associated disorders may be caused by the same brain abnormalities or metabolic defects that cause the epilepsy. Understanding why these disorders often overlap with epilepsy and how they affect treatment and self-management is critical for improving medical care.

Short Term

1. For the general population of people with epilepsy, describe the type, frequency, and severity of the medical conditions that often occur with epilepsy.
2. Identify at least one new risk factor that increases the likelihood that someone with epilepsy will develop cognitive problems (problems with thinking, learning, or memory). Do the same for mental health or behavioral conditions such as depression, attention deficit disorder or autism, as well as other medical conditions.

Long Term

1. Describe the usual course of each condition associated with epilepsy. Explain the nature of the relationship between each condition and the underlying causes of epilepsy, the clinical features of the epilepsy syndrome associated with it, and available treatments.

B. Identify the predictors [the early symptoms or indicators of a disease] and biological mechanisms that contribute to the development of each medical condition associated with epilepsy.

Background: To effectively treat epilepsy in people who also have associated medical conditions, scientists will need to understand how one disease affects the other. Discovering methods to determine the influences of one disease upon another, using that knowledge to develop treatments, and then testing those treatments in animal and human models, will lead to more effective therapies for epilepsy when it occurs with other disorders.

Short Term

1. Identify promising techniques and models used in other areas of neuroscience research (such as imaging technologies or methods used in genomics studies) and use at least two of them to study cognitive and behavioral conditions associated with epilepsy.
2. Develop and test at least one animal model of epilepsy and an associated condition.
3. Develop and put into use a standardized method for evaluating whether the therapies or medications used to treat epilepsy have a positive or negative effect on the cognitive, mental health, or behavioral conditions associated with epilepsy.

Long Term

4. Determine how the biological mechanisms that drive the development of epilepsy contribute to the development of associated conditions.

5. Determine if the biological mechanisms, symptoms, and course of disease of cognitive, mood, or attention disorders in people with epilepsy are the same as in those without epilepsy.

C. Determine the best treatments for the cognitive, mental health, or behavioral conditions associated with epilepsy.

Background: People with epilepsy have an increased risk for depression and anxiety. Further research could tease out the contributions of social problems, stress, or neurotransmitter abnormalities to the development of these kinds of disorders and epilepsy.

Short Term

1. Determine if the treatment regimens for at least two of these conditions in people without epilepsy are also effective in people with epilepsy, or if conditions associated with epilepsy require different strategies.
2. Develop at least one successful care model for the diagnosis and treatment of people with epilepsy and an associated medical condition. Show that it improves outcomes.

Long Term

3. Develop and test new treatment and management strategies for people with epilepsy and associated cognitive, mental health, or behavioral disorders who are not being adequately treated with current therapies.

D. Prevent or reduce other harmful conditions that occur in people with epilepsy.

Background: Some people with epilepsy are also at risk for other conditions such as sudden unexplained death (SUDEP). Research into the conditions that complicate epilepsy treatment will offer scientists ways to prevent these conditions from happening or successfully treat them if they appear.

Short Term

1. Sudden unexplained death in epilepsy (SUDEP)
   a. Develop and test at least one prevention strategy to lower the number of people with epilepsy who experience SUDEP.
2. Sleep disturbances
   a. Identify sleep disorders that are associated with epilepsy and establish, for each, how frequently they occur.
   b. Determine how sleep disorders affect the frequency of seizures.
   c. Describe the impact of sleep disorders on at least one of the medical conditions associated with epilepsy.

Long Term

3. Sudden unexplained death in epilepsy (SUDEP)
   a. Discover the biological mechanisms that cause SUDEP. Describe the effects of seizures on breathing, heart rate, and other functions of the autonomic nervous system.
4. Identify the best ways to avoid systemic disorders associated with epilepsy and its treatment, such as low bone density, hormonal imbalances, and birth defects.

E. Develop effective methods for diagnosing, treating, and preventing non-epileptic seizures (NES).

Background: Non-epileptic seizures often look like epileptic seizures but are not associated with seizure-like brain activity. Looking at how and why these seizures occur will help researchers understand how they can be prevented and treated.

1. Determine the types of NES and how often they occur in the general population, compared to people with epilepsy.
2. Discover and describe common risk factors and causes of NES.
3. Test at least one effective treatment for NES.