

2010 Epilepsy Research Benchmarks Progress Update (2007-2009)

Overview

Since the development of the [2007 Epilepsy Research Benchmarks](#), remarkable strides have been made toward understanding the causes of epilepsy and epileptogenesis, developing new and improved treatments, and delineating factors that contribute to comorbidities associated with epilepsy. The Epilepsy Research Benchmarks Stewards have selected the following research advances from 2007-2009 as examples of important progress toward meeting goals within the 2007 Epilepsy Research benchmarks. (Stewards and other researchers who contributed to this report are acknowledged below.) These advances resulted from research conducted in the U.S. and abroad and include numerous findings reported by the Stewards themselves. Financial and other support for the investigators and projects that made these advances was provided by NINDS, other NIH institutes, and additional U.S. government partners; as well as by nongovernmental organizations including the Epilepsy Foundation, Citizens United for Research in Epilepsy (CURE), the Tuberous Sclerosis Alliance, the Epilepsy Therapy Project, and the American Epilepsy Society, among many others.

Although the findings in these summaries hold much promise for reducing the burden of the epilepsies, many research needs remain unmet. In particular, biomarkers and new and improved animal models are needed to aid the search for strategies to prevent epilepsy and to treat epilepsies that remain intractable to currently available interventions. The comorbid conditions common in people with epilepsy were a new focus for the Epilepsy Benchmarks in 2007, and many questions have yet to be answered about the interplay between these conditions, seizures, and the underlying causes of epilepsy. Moving forward, NINDS and the Benchmarks Stewards will continue to monitor research across all Benchmarks areas and to promote further progress in areas of need. Among current opportunities, continued advances in technologies for genetics research, brain imaging, and electrophysiological recording stand to accelerate the pace of discovery. New resources and infrastructure for collaborative approaches also present research opportunities, as do recent insights from other disorders that share features with the epilepsies.

Area I: Prevent epilepsy and its progression

A. Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious).

Background:

Epilepsy has many causes. It may be the result of developmental problems due to genetic mutations that interfere with the normal wiring and activity 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.

Summary of advances:

Neurons rely on ion channels in their cell membranes to generate electrical activity and on signaling molecules called neurotransmitters to propagate this activity from one neuron to another. Mutations affecting ion channels and cell-surface receptors for neurotransmitters disrupt neuronal activity and communication, and many such mutations are known to cause different forms of epilepsy. However, more recent research points to genetic variations affecting other processes not previously linked directly to epilepsy. For example:

- Early infantile epileptic encephalopathy with suppression-burst (EIEE), a severe form of early onset epilepsy, has recently been associated with mutations in the gene *STXBP1* (or *MUNC18-1*). The protein encoded by this gene, synaptic binding protein 1, is involved in the release of neurotransmitter molecules from neurons [1].
- A study of epilepsy and mental retardation limited to females (EFMR) led to the identification of mutations in the gene *PCDH19*, which encodes protocadherin 19, a member of a large group of proteins important in the development of neuronal connectivity in the brain[2].
- Neurons communicate through both excitatory signaling, which increases a neuron's activity, and inhibitory signaling, which decreases activity. Several recent studies have added to a growing recognition of a role for impaired development of inhibitory neuronal connections and inhibitory signaling in epilepsy [3-10].

Infectious and immune processes are known to contribute to some forms of epilepsy, but a number of recent reports have provided new insights into the mechanisms involved and opportunities for studying the interaction between environmental and genetic risk factors in epilepsy.

- New reports of acute viral infections by the H1N1 flu virus [11] and respiratory syncytial virus (RSV) [12] with acute seizures raise questions about the extent to which these infections will be associated with future epilepsy (or other neurologic disease). Another study found that maternal genitourinary infection during pregnancy was associated with an increased risk of epilepsy in children [13].
- Recent research has suggested that human herpesvirus-6 (HHV-6) may be involved in the pathogenesis of a type of epilepsy known as mesial temporal lobe epilepsy (MTLE) with mesial temporal sclerosis [14]. This virus has been associated with childhood febrile seizures, and its potential role is under further investigation in an ongoing multicenter study to understand the relationship between febrile seizures and later development of MTLE [15].
- Autoimmune-mediated limbic encephalitis can lead to epilepsy. Prior research has emphasized paraneoplastic causes, in which the body's immune response to a tumor cross-reacts with proteins normally expressed in the brain, which then become the target of an autoimmune attack. However, recent case reports are raising awareness of non-paraneoplastic autoimmune-mediated limbic encephalitis and seizures [16].

B. Identify underlying mechanisms of epileptogenesis.

Background:

Epileptogenesis refers to the process through which brain tissue develops the tendency for spontaneous and chronic seizures. A better understanding of where, how, when, and why epileptogenesis occurs will help researchers answer fundamental questions about how epilepsy develops and persists as a chronic disease and may also point to opportunities to intervene.

Summary of advances:

Recent research has pointed to a number of mechanisms contributing to epileptogenesis, including changes in ion channels and neurotransmitter receptors that mediate neuronal excitability, cell signaling pathways in neurons and other types of brain cells, and immune and inflammatory processes. (Also see Area ID for examples of research targeting these mechanisms for the development of therapeutic interventions.) Notable findings include:

- The mammalian target of rapamycin (mTOR) pathway regulates many important physiological processes, such as protein synthesis, metabolism, and the function of synapses – the sites of communication between neurons. Studies have shown that the mTOR pathway contributes to epileptogenesis in animal models of Tuberous Sclerosis (TSC), status epilepticus, and epilepsy due to traumatic brain injury (post-traumatic epilepsy). In addition, correlative evidence suggests a role for the mTOR pathway in human epilepsies, including TSC, focal cortical dysplasia, and ganglioglioma. These findings [17-26] have direct therapeutic applications, as an FDA-approved drug, rapamycin, exists and could be tested in anti-epileptogenic clinical drug trials.
- The blood-brain barrier (BBB) serves an important function in selectively regulating which substances can access the brain, ideally allowing vital nutrients in while keeping potentially damaging agents out. However, a breakdown of the BBB can occur under a variety of conditions that lead to inflammation in the brain, such as stroke, central nervous system (CNS) infection, head trauma, and neurodegenerative diseases. Accumulating evidence indicates a role for BBB breakdown [27-32] and inflammation more generally [33-37] in promoting epileptogenesis, and several recent studies have begun to elucidate the mechanisms involved.
- Non-neuronal cell types in the brain called glia, long-viewed as passive support cells, are now acknowledged to have a variety of functions that directly affect brain excitability and signaling. In addition to playing integral roles in blood-brain barrier maintenance and inflammatory responses mentioned above, glia participate in other mechanisms relevant to epileptogenesis, such as neurogenesis, neuronal migration, synaptic development and plasticity, non-synaptic communication with neurons, regulation of neurotransmitter and ion levels, and direct release of neurotransmitter-like substances. Therapeutic strategies targeting glia-specific processes could

potentially have good efficacy, but fewer side effects, than traditional treatments that primarily target neurons [38, 39].

- Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian central nervous system. However, during nervous system development, GABA exposure instead excites certain neurons. This early GABA-mediated excitation is important for brain development but also contributes to an increased susceptibility to seizure generation in the immature brain. New research now suggests a role for GABA-mediated excitation in seizures and epilepsy that may not be restricted to early developmental ages. Studies using surgically removed brain tissue from epilepsy patients show a bias toward GABA-mediated excitation in brain regions involved in temporal lobe epilepsy or intractable focal epilepsies due to cortical malformations [40, 41]. These findings [40-51] point to the potential for therapeutics for epilepsy and epileptogenesis in infancy and beyond that target mechanisms known to mediate the switch from GABA-mediated excitation to inhibition.
- Other recent research findings have continued to demonstrate the importance of ion channels in epilepsy, and they have also highlighted their roles in novel mechanisms of epileptogenesis [40, 43, 47, 52-59]. For example, one study has shown that a type of calcium ion channel (T-type calcium channels) previously linked to absence epilepsy also mediates epileptogenesis in a model of limbic epilepsy [52].

C. Identify biomarkers for epileptogenesis.

Background:

Biomarkers are biological markers indicating changes in cells, tissues, or organs that are associated with the development or progression of a disease. Biomarkers for epileptogenesis could be used to identify people who are at higher than average risk of developing epilepsy and could also facilitate research to develop antiepileptogenic therapies by serving as markers of treatment response.

Summary of advances:

With new and improved technologies for imaging the brain and recording brain activity at increasingly fine scales, researchers are identifying structural and functional changes associated with or predictive of seizure generation and epileptogenesis. Examples of recent advances and ongoing research on potential biomarkers revealed through these new approaches are:

- Studies in both animal models of mesial temporal lobe epilepsy and in patients with focal epilepsies have shown that a type of high frequency oscillation in brain activity called fast ripples can identify epileptogenic areas. Ongoing studies are investigating the potential for fast ripples to also predict the development of epilepsy as well as the subsequent frequency of seizure generation [60].
- In previous research, magnetic resonance imaging (MRI) following experimentally induced seizures in rats has shown that structural abnormalities in the hippocampus, a brain region involved in temporal lobe epilepsy, predict the subsequent development of spontaneous seizures [61]. Studies are now underway to determine whether similar changes predict the development of epilepsy after prolonged febrile seizures in children [15]. Structural MRI in patients with mesial temporal lobe epilepsy has also identified patterns of hippocampal and neocortical tissue loss that may predict disease progression, resistance to pharmacological treatment, or postoperative outcome [62].

D. Identify approaches to prevent epilepsy or its progression

Background:

Antiepileptic drugs are currently used to control the seizures of people with epilepsy. However, not everyone responds well to the drugs, which can also have troublesome 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 or its progression once it has begun.

Summary of advances:

Studies in experimental animal models of different forms of acquired epilepsy have identified a number of putative epileptogenic mechanisms occurring during the latent period between an initial insult and the development of spontaneous seizures. Recent advances suggest these mechanisms may be useful targets for the development of antiepileptogenic interventions. Additional studies have begun to identify and develop preventive approaches for epilepsies known or presumed to result from genetic mutations or brain malformations. (Also see additional references [63-66] and Area IB for epileptogenic mechanisms that may be targets for intervention.)

Acquired epilepsies:

- Neurotrophic factors (NTFs) are proteins known to promote the growth and survival of neurons, and they represent an intrinsic repair mechanism in the brain that may be targeted to protect against neuronal damage and loss following an epileptogenic insult. In a rat model of acquired temporal lobe epilepsy, supplementing fibroblast growth factor-2 (FGF-2) and brain-derived neurotrophic factor (BDNF) reduced the frequency and severity of spontaneous seizures [67].
- Building on the hypothesis that BBB breakdown contributes to trauma-induced epilepsy, a recent study in rat brain tissue focused on gene expression and other changes induced by a blood protein called albumin, which can leak into the brain following BBB breakdown [27]. The study showed that blocking a signaling pathway activated by albumin suppressed most albumin-induced changes in gene expression and also prevented the development of epileptiform activity. Additional studies have also shown antiepileptogenic effects by blocking other mechanisms triggered by BBB disruption and inflammation. (See Area IB.)
- Astrogliosis, or the activation and proliferation of glial cells called astrocytes, has been associated with epilepsy in both animal models and people. Studies in mice provide evidence that astrocyte-dependent regulation of adenosine, an inhibitory modulator of neuronal activity, links astrogliosis to development of epilepsy and also point to the potential antiepileptogenic benefit of approaches that augment adenosine [68].

Dysplastic and genetic epilepsies:

- In a mouse model of TSC, the FDA-approved immunosuppressant drug rapamycin suppressed seizures, reversed structural changes in the hippocampus and cortex, and also improved behavior [22, 69]. Importantly, studies in animal models of acquired temporal lobe epilepsy showed that the epileptogenic potential of rapamycin may extend beyond TSC [17, 25]. (See also Area IB.)
- In an animal model of absence epilepsy, treatment with the anticonvulsant drug ethosuximide prevented the development of spontaneous seizures [70]. Interestingly, this model displays features consistent with depression as a comorbidity, and ethosuximide treatment also prevented development of depression-like symptoms [71]. (See also IIIB.)

E. Develop new animal models to study epileptogenesis

Background:

Animal models for different types of epilepsy can help to answer questions about how epilepsy develops and how repeated seizures affect brain structure and function. They are also essential tools for the development and preliminary testing of new therapies to prevent epileptogenesis or the progression of epilepsy.

Summary of advances:

Recognizing that the epilepsies represent a heterogeneous class of disorders, researchers are developing a range of animal models that mimic different types of epilepsy in order to better investigate their underlying mechanisms and to test potential interventions to prevent epileptogenesis. Some examples of recently developed models include:

- Infantile spasms (IS) are one of the most devastating epileptic encephalopathies of infancy, typically evolving to mental retardation and other types of often intractable epilepsies. Classical antiepileptic drugs (AEDs) are not generally sufficient to treat IS, and prolonged treatment with hormones or the drug vigabatrin is not only costly but

associated with toxic side effects. A number of recently reported chronic and acute models of IS may help to better understand this syndrome and identify more effective and safer therapies [7, 9, 72-74].

- Infections of the central nervous system increase the risk for development of seizures and epilepsy. Previous research had shown that infection in mice with Theiler's murine encephalomyelitis virus (TMEV) causes acute seizures. New findings show that TMEV chronically altered seizure susceptibility in mice, suggesting a new model for studying the development of epilepsy after infection [75].
- Studies of an animal model of Alzheimer's disease (AD) (human amyloid precursor protein transgenic mice) have shown that these animals express high levels of amyloid-beta peptides [76] and also exhibit spontaneous nonconvulsive seizure activity in the cortex and hippocampus. More recent studies speculate that high levels of amyloid beta in the brain cause the recurrent epileptiform activity and cognitive deficits in humans [77].

F. Test the efficacy of prevention strategies

Background:

New antiepileptogenic therapies must prove their effectiveness in clinical trials before they can be used in for the prevention of epilepsy in people at risk.

Summary of Advances:

- Although a number of studies have begun to test potential antiepileptogenic interventions in animal models (see Area ID), many approaches under development have not yet been tested in people at risk for developing epilepsy. However, a preliminary clinical report suggested rapamycin might prevent epileptogenesis in people with TSC [78], consistent with its effects in an animal model of the disease. In addition, clinical trials are ongoing for the prevention of epilepsy following traumatic brain injury, including "Preventing Epilepsy after Traumatic Brain Injury with Topiramate," (University of Pennsylvania, [NCT00598923](#)) and Federal University of Sao Paulo in Brazil study "Use of Biperiden for the Prevention of Post-traumatic Epilepsy" (Federal University of São Paulo, [NCT1048138](#)).

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy.

A. Identify basic mechanisms of seizure generation (ictogenesis) that will lead to the development of cures.

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.

Summary of advances:

A number of recent investigations into the biological mechanisms that cause seizures have focused on using electrophysiological and computational methods to understand which neurons are involved initiating seizures. Other studies have centered on the cell-signaling pathways that are involved in propagating and terminating seizures. A few examples are:

- A number of important computational studies have led to the hypothesis that “hub cells” (cells with a large number of inputs and outputs) may contribute to seizure initiation. The hypothesis suggests that an increase in connectivity of just a small number of cells in a circuit is sufficient to trigger synchronous activation in the network, contributing to hyperexcitability and an increased probability of seizure activity. Understanding which cells initiate seizures will help researchers develop therapies that specifically target these cells [79-81].
- Epileptiform activity requires large amounts of energy in the form of glucose. Glucose and its metabolites are transported from blood vessels to distant neurons through networks of glial cells coupled to each other by gap junctions, which are protein channels that allow small molecules to pass between cells. During periods of prolonged activity, there is a neurotransmitter-dependent increase in coupled astrocytes that facilitates delivery of these energetic metabolites to neurons. Blocking this process can prevent epileptiform activity. These findings suggest that molecular targets on astrocytes might be an important approach to seizure control [82].
- Acidosis produced, for example by CO₂ inhalation, is well known to suppress or truncate seizures. Recent studies have revealed that the Acid Sensing Ion Channel 1a (ASIC1a) likely plays a key role in seizure termination. These findings indicate that ASIC1a is part of a feedback inhibitory system that is activated by seizures and serves to limit seizure severity and duration. This finding is significant because it provides a logical basis for identifying ASIC1a potentiators for treating status epilepticus and perhaps tonic-clonic seizures [83].

B. Develop tools that facilitate the identification and validation of a cure.

Background:

Research and diagnostic tools such as animal models, biomarkers, and screening techniques facilitate efforts to identify, develop, and test new therapeutic interventions for epilepsy, and they may also inform predictions about which individuals may respond best to which treatments.

Summary of advances: The epilepsies are a group of disorders with diverse causes and clinical presentations. This diversity means that a variety of treatment options need to be available. Furthermore, variations in the genetic background of individual people with epilepsy may also affect their responses to different treatments. The examples below highlight advances in identifying new drug targets, understanding and localizing seizure-related brain activity, and screening patients for predictors of treatment response.

- Neurotoxicity caused by reduced blood flow and oxygen deprivation to the brain, as occurs in stroke or neonatal hypoxia-ischemia, can lead to seizures and the development of chronic epilepsy. One contributor to increased seizure susceptibility in neonates is a high level at young ages of receptors in neurons for the excitatory neurotransmitter glutamate, which can lead to excessive neuronal activity. A study in a rat model of neonatal seizures showed that drugs that block a type of glutamate receptors called AMPA receptors reduced H-I seizures and subsequent cognitive deficits [84].

- As epilepsy is a disorder highlighted by synchronous activation of neurons, it comes as no surprise that most therapeutic approaches to date have focused on neuronal activity (e.g., sodium channel blockers, enhanced inhibition through GABA_A receptors, etc.). However, over the past few years, interest in the effects of brain inflammation and immune processes on seizure generation (as well as epileptogenesis, see Area I) has attracted much attention. For example, based on research in animal models, drugs that target two particular immune signaling molecules, ICE/caspase 1 and IL-1 β receptors, show promise as antiepileptics [84-86].
- Recent innovations in intracranial recording technologies, such as microarray electrodes for recording high resolution EEG and single neuron activity, have led to the detection of previously uncharacterized electrical events in patients with intractable epilepsy, including microbursts, microseizures, and high frequency oscillations. These patterns of neuronal activity may be valuable biomarkers for localizing epileptogenic networks and understanding seizure generation. Moreover, they may also inform the development of methods to predict the occurrence of seizures based on brain activity patterns that precede their onset [87-93]. (See also Area IC.)
- Molecular biomarkers have proven useful for the identification of patients most at risk for adverse drug reactions. A recent study identified a specific gene that makes carbamazepine, a commonly used antiepileptic drug, risky for some populations of patients. The authors report a strong risk for serious and potentially fatal skin reactions to carbamazepine in the subgroup of Asian individuals with the HLA-B*1502 allele [94]. As a result of this finding, the FDA has recently relabeled carbamazepine with a recommendation to evaluate patients with ancestry across broad areas of Asia, including South Asian Indians, for this genotype and to avoid the use of carbamazepine in those who test positive.

C. Optimize existing therapies and develop new therapies and technologies for curing epilepsy.

Background:

Available antiepileptic medications fail to adequately control seizures in as many as one third of people living with epilepsy, and even when seizures are controlled, long- and short-term side effects of drugs or surgical interventions can further diminish quality of life.

Summary of advances:

Improvements in current treatments and the development of new therapies focus largely on ways to more specifically target epileptic tissue and cellular pathways. These include advances in presurgical imaging techniques to more accurately identify epileptic areas of the brain for surgical removal and improvements in drugs and drug delivery methods. Furthermore, clinical trials to test new antiepileptic drugs and efforts to develop and test non-standard treatment approaches are ongoing.

- Resective epilepsy surgery remains an established treatment with the potential to permanently arrest seizures in some patients with medically resistant epilepsy. However, this option is limited to people whose seizure focus can be clearly localized and removed without functional loss that outweighs the benefits of reduced seizure frequency. Better ways to localize seizure-generating brain regions could identify more candidates for surgical intervention and improve the success of resective surgery while minimizing cognitive deficits. Toward this end, the examples below highlight advances in magnetic resonance imaging (MRI), magnetic source imaging (MSI) and magnetoencephalography (MEG) technologies, as well as in the analysis of data from these technologies [95-110]. (Also see Area IIIC for further discussion of mapping functional networks in candidates for epilepsy surgery.)
- Brain stimulation to prevent or halt seizure activity may provide a viable and effective epilepsy treatment. Efforts are underway to develop and test responsive devices that couple seizure detection and prediction algorithms to electrical stimulation (see Area IIB). Several ongoing clinical trials that test a variety of surgical and stimulation protocols show a statistically significant reduction in seizure frequency [111]. While these early results are promising, seizure freedom has not been achieved, and further studies will be necessary to refine stimulation parameters [112-116].

- On the cutting edge of new experimental therapeutic strategies are gene therapies, in which genes are delivered to the affected tissue to replace defective genes or enhance the expression of proteins that reduce excitability. Neuropeptide systems, such as NPY and galanin, adenosine, and inhibitory neurotransmitter (GABA) signaling pathways are the most popular targets. These strategies have proved effective in animal models, though in general they are not yet ready for clinical application. Current advances in the use of viruses to deliver genes to affected tissues show promise and may move the clinical application of gene therapy forward [117-121].
- Some antiepileptic compounds cannot be delivered systemically, either because of side effects or because they do not readily cross the blood-brain barrier. Strategies that show promise for improving drug delivery involve the implantation of a catheter to chronically infuse a drug or the implantation of matrices embedded with the drug or with cells engineered to produce large quantities of the compound. Further studies are necessary to determine whether these strategies will be clinically beneficial [122-124].
- Significant progress has been made in the clinical testing of new pharmacological treatments. Phase II/III clinical trials are ongoing or have been completed for several antiepileptic drugs, including retigabine, carisbamate [125], brivaracetam [126, 127], rufinamide [128, 129], lacosamide [130, 131], ganaxolone [132, 133], and eslicarbazepine acetate [134, 135]. A number of other compounds are in earlier stage development, poised to enter either phase II or phase III clinical trials [136, 137].
- In addition to traditional drug trials, randomized, placebo-controlled trials were undertaken for alternative, non-drug therapies. Examples include trials of the ketogenic diet (high-fat, adequate-protein, low-carbohydrate) [138-140], yoga [141], P- glycoprotein blockers [142], and polyunsaturated fatty acids [143].
- Moreover, building on the recognition that patients with drug-resistant epilepsy may achieve seizure control with the ketogenic diet, recent studies have further investigated the potential of pathways involved in energy metabolism as targets for new pharmacological therapies [144-146]. A preliminary clinical trial planned to begin in 2010 will assess the tolerability and efficacy of 2-deoxy-D-glucose (2DG), an analogue of normal sugar that blocks sugar metabolism, for seizure reduction in patients with intractable temporal lobe epilepsy.

Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment.

A. Identify and characterize the full range and age specificity of comorbidities in people with epilepsy.

Background:

Compared to those without epilepsy, people with epilepsy are more likely to develop or report certain neuropsychiatric conditions, including depression, anxiety, sleep disturbances, cognitive impairment, and psychosis, as well as poor physical health outcomes, such as pain and arthritis, heart disease, and even sudden unexpected death. Research suggests that the presence and severity of these conditions varies across individuals and different types of epilepsy. Better characterization of the comorbid conditions of epilepsy will advance our understanding of their causes and risk factors.

Summary of Advances:

Several recent studies have provided new information on the range and frequency of conditions beyond seizures affecting both adult and pediatric populations of people with epilepsy. This research is also providing insights into factors that affect individuals' susceptibility for developing certain comorbidities.

- Community-based and broad population studies have found that adults diagnosed with epilepsy are more likely than people without epilepsy to report anxiety, depression, or suicidal behaviors [147, 148]. A population-based survey in 19 U.S. states found that adults with active epilepsy or a history of epilepsy were more likely to report worse health-related quality of life [149], and a retrospective study found that a prior history of psychosis was more common in cases of new-onset epilepsy than in people without epilepsy [150].
- A longitudinal study of children with newly diagnosed epilepsy found that approximately one in four showed below normal cognitive function. Factors associated with poorer cognitive function in this and other research included young age at epilepsy onset, symptomatic cause (due to an insult or an underlying cause like abnormal brain development), and continued treatment [151, 152]. Additional studies reported deficits in attention, cognition, and neuropsychological function in children at the onset of seizures [153, 154] and associated the presence of comorbid cognitive and behavioral deficits at epilepsy onset with worse prospective cognitive development [155].

B. Identify predictors and underlying mechanisms that contribute to co-morbidities.

Background:

In the past, cognitive and behavioral comorbidities of epilepsy have been viewed largely as consequences of seizures that would disappear with adequate seizure control. However, this view has been challenged by more recent findings that these conditions may be present at or before the onset of epilepsy and that they do not always or fully improve with seizure control.

Summary of Advances:

Research in people and animal models is advancing our understanding of the factors that contribute to comorbidities, which could include shared mechanisms that cause both seizures and other conditions, neurobiological effects of recurrent seizures, side effects of anticonvulsant medications, and psychological responses to living with epilepsy. Some recent findings are highlighted below; for additional references, see [156-163].

- Advancing technologies for imaging and recording brain structure and function are providing new clues into the neurobiological basis of cognitive and behavioral impairments that can accompany epilepsy [164-176]. For example, one brain imaging study found that compared to age-matched controls, children with new onset epilepsy showed a delayed developmental increase in white matter volume, which contains neuronal fibers connecting brain regions [177]. Another study using a technique called transcranial magnetic stimulation (TMS) showed evidence for altered brain excitability up to 24 hours before and after a generalized tonic-clonic seizure, suggesting a potential basis for cognitive impairment that can accompany poorly controlled epilepsy [178]. Several studies using positron emission tomography (PET) imaging have shown evidence for altered signaling by the neurotransmitter serotonin, suggesting a mechanism in common with primary major depressive disorders [165, 179]. The continued application of these

new technologies, particularly in research that combines multiple measures of brain structure and function, is a promising area of research toward understanding the comorbidities of epilepsy.

- Repeated seizures in childhood have been associated with later cognitive and behavioral deficits, but the roles of the seizures themselves or other underlying mechanisms are unclear. In children with prior epilepsy but otherwise normal neurological exams and average or above average intelligence, even after the resolution of seizures, information processing speed remained significantly lower than in siblings without a history of epilepsy [180]. Rats subjected to experimental seizures early in life showed spatial memory deficits and abnormal activity in neurons important for mapping and retrieving spatial information [181, 182]. In addition, learning and memory deficits in rats with prior febrile seizures correlated with changes in the hippocampus visible on MRI brain scans, suggesting potential biomarkers for lasting deficits following prolonged seizures early in life.
- Temporal lobe epilepsy (TLE) is the most common form of non-acquired, focal epilepsy in adults and is often associated with cognitive deficits. In a rat model of TLE, pharmacologically inducing an initial prolonged seizure (status epilepticus) leads to a period of epileptogenesis, and then to chronic, spontaneous seizures. Longitudinal assessments on memory tasks during epileptogenesis in this model showed impaired spatial memory and soon after status epilepticus, occurring before the onset of spontaneous seizures and persisting into the chronic seizure stage without further change [183]. A longitudinal study of people with TLE showed evidence for hindered cognitive development but not for ongoing progressive decline following TLE onset [184], and a study in children suggested that early TLE may impair the development of processes important for modulation of memory by emotional information [185].
- Research in populations with other conditions that often overlap with epilepsy, such as autism and Fragile X Syndrome, can also shed light on the basis of cognitive and behavioral comorbidities. Genotype-phenotype analysis showed an over-representation of seizures among symptoms previously reported in association with genetic loci linked to autism [186], and a large population-based study found that CNS hemorrhage, edema, and seizures in pre-term infants were associated with the later development of autism [187].

C. Determine the optimal treatments for the neuropsychiatric and cognitive co-morbidities in people with epilepsy.

Background:

Efforts to develop treatments for the epilepsies must extend beyond controlling or preventing seizures to include ameliorating the cognitive, behavioral, and emotional difficulties that are increasingly recognized as part of the spectrum of challenges affecting quality of life for people with epilepsy.

Summary of Advances:

Some recent reports have drawn on existing research to suggest guidelines for the diagnosis and treatment of comorbidities in epilepsy. In addition, by identifying the underlying mechanisms of the cognitive and behavioral comorbidities of epilepsy, research in people with epilepsy and in animal models is also suggesting new strategies to treat or prevent these deficits.

- An expert panel of members of the Epilepsy Foundation's Mood Disorders Initiative published a consensus statement on the evaluation and treatment of people with epilepsy and affective disorders, with a particular focus on depression [187, 188]. The goals of the statement were to begin to address needs for improving treatment of depression in people with epilepsy by providing information to clinicians about the condition and current barriers to treatment, and by making recommendations on treatment options. In the area of attention deficit hyperactivity disorder (ADHD), recent studies suggest that methylphenidate is similarly effective for treating ADHD in children with and without epilepsy [189, 190].
- In a rat model of TLE, an important component of inflammatory signaling pathways called interleukin 1beta (IL-1 β) has been implicated in both the development of seizures and as a mediator of depression. Blocking the actions of IL-1 β improved measures of depression in this model, suggesting a therapeutic role for inhibitors in this pathway [191]. In another study, treatment with the anticonvulsant drug ethosuximide improved measures of depression in a

rodent model of absence epilepsy [71] (see also mention of this model in Area I). In mouse models of TSC, both learning and memory impairments and epilepsy improved after treatment with rapamycin, a drug that inhibits the mTOR signaling pathway implicated in this disorder [26, 192].

- Research in people who undergo surgery to treat intractable epilepsy is also leading to a better understanding of the brain networks that underlie language and memory impairments in this population. Understanding these networks – through behavioral testing, new imaging technologies, microelectrode recordings, functional connectivity studies, and cortical surface mapping – could improve predictions for who is at risk for postoperative or natural decline. It could also alter treatment approaches to avoid such decline, by for example, offering surgery earlier for some patients, altering surgical approach to avoid functional networks, or improving methods of presurgical functional mapping [193-206].

D. Prevent or limit other adverse consequences occurring in people with epilepsy.

Background:

Some people with epilepsy are also at risk for other types of conditions beyond behavioral and cognitive comorbidities, including sudden unexpected death in epilepsy (SUDEP), sleep disturbances, and systemic problems affecting bone health and hormonal and reproductive function.

Summary of advances:

SUDEP is defined as the “sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death in a patient with epilepsy where the postmortem examination does not reveal a toxicologic or anatomic cause of death, with or without evidence of a seizure and excluding documented status epilepticus” [207]. Recent research advances toward understanding the causes of SUDEP and efforts to raise awareness and work toward prevention include:

- Two recent clinical studies characterized adverse effects on respiration by seizures and found that both partial and generalized seizures could lead to reduced blood oxygen levels [208, 209]. In many cases, reduced oxygen saturation was associated with central apnea, or temporary loss of signaling between the brain and the muscles that control breathing. These findings are relevant to case reports suggesting central apnea as one mechanism in SUDEP, and to the known high risk of SUDEP in uncontrolled generalized convulsions. Other clinical studies have reported changes in cardiac function in people with epilepsy that may be associated with SUDEP [210-215].
- Epilepsy has been observed in a mouse model with mutations in a gene that causes sudden cardiac death in humans [216]. This animal model provides evidence that genes and mutations underlying potentially fatal cardiac defects may also be present in human epilepsy, suggesting a potential risk factor for SUDEP in some people with epilepsy. Also in SUDEP animal model research, some studies have focused on changes in autonomic nervous system function [217], and another pointed to a role for overactivation of adenosine receptors after seizures and to caffeine as a potential preventive intervention [218]. As a possible primate model, sudden unexpected and unexplained death was observed in a research colony of baboons studied as models of primary generalized epilepsy [219]. Postmortem analyses revealed lung defects with similarities to some human SUDEP cases.
- The American Epilepsy Society and the Epilepsy Foundation have established a Joint Task Force on SUDEP, the first organized effort of major epilepsy organizations to raise awareness of and solve the problem of SUDEP. The Task Force was convened to assess current knowledge about SUDEP, and to recommend ways to work towards its elimination [220]. One outcome was a 2008 NINDS-sponsored workshop on SUDEP, attended by national and international clinicians, researchers, patient advocates, and ethics and legal experts. In addition, Citizens United for Research in Epilepsy (CURE) recently established a new grant program targeting SUDEP research.

Prior research has suggested that epilepsy is associated with sleeping disturbances such as interrupted, insufficient, or poor quality sleep, obstructive sleep apnea, and excessive daytime somnolence; and that sleep disturbances among people with epilepsy may be a risk factor for poor seizure control. Recent noteworthy studies to better determine the prevalence of such sleep disturbances and their relationship to the clinical course of epilepsy include:

- In terms of prevalence, compared to children without epilepsy, one study found that children with epilepsy had, on average, a significantly higher frequency of sleep problems (falling asleep before being put to bed, prolonged time to fall asleep after being put to bed, nocturnal awakenings, daytime sleeping, and others) [221]. In another study of adult epilepsy outpatients, insomnia was found in 25%, obstructive sleep apnea in 28%, and excessive daytime somnolence in 17%, with the latter in particular associated with lower quality of life [222]. A study in older adult patients with epilepsy found undiagnosed REM sleep behavior disorders (RBD) in 12.5% subjects studied. RBD episodes may be misinterpreted as seizures, and these results suggest screening for RBD may be important in older patients with epilepsy reporting nocturnal seizures [223].
- Other studies are beginning to shed light on how sleep disorders may affect the occurrence of seizures in people with epilepsy. For example, compared to patients whose seizures were in remission or had recently improved, those with relatively recent seizure onset or exacerbation were substantially more likely to have obstructive sleep apnea. The results of this small case-control study suggest that obstructive sleep apnea may be a causal factor in worsening seizures in older adults with epilepsy [224]. A small pilot trial in adult patients with both refractory epilepsy and obstructive sleep demonstrated the feasibility of a larger, definitive clinical trial to test the hypothesis that continuous positive airway pressure (CPAP) treatment may reduce seizures [225].

The examples below highlight recent and ongoing research activities focused on the developmental outcomes of offspring born to mothers with epilepsy, as well as efforts to develop practice guidelines and recommendations for improving the treatment of epilepsy during pregnancy.

- With support from the Epilepsy Therapy Project and the Milken Foundation, the Healthy Outcomes for Pregnancies in Epilepsy ([HOPE](#)) project was an international expert panel convened to discuss current knowledge and needs related to strategies to improve pregnancy outcomes in women with epilepsy [226-231]. In addition, the American Academy of Neurology and the American Epilepsy Society jointly conducted three evidence-based systematic reviews of pregnancy-related studies among women with epilepsy resulting in recommendations for pregnancy counseling and care in women with epilepsy, and for additional research needs [232-234].
- The NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study enrolled pregnant women with epilepsy who were taking a single antiepileptic agent in a prospective multi-center study in the U.S. and the U.K. An interim analysis of cognitive outcomes in 309 children at 3 years of age found that those exposed to valproate during pregnancy had significantly lower IQ scores than those exposed to other antiepileptic drugs [235]. In other research, a study in a rat model of TLE suggested that maternal epilepsy itself may not be detrimental to the developing fetus [236].
- The [North American Pregnancy Registry](#) was established to obtain and publish information on the frequency of major malformations, such as heart defects, spina bifida and cleft lip, among infants whose mothers had taken one or more antiepileptic drugs to prevent seizures or to treat any other medical condition. As of May 2010, enrollment in the registry included 7537 pregnancies in the U.S. and Canada.

Although bone health problems have been reported in people with epilepsy, it remains unclear whether they are due to antiepileptic drug (AED) use, which could adversely affect bone metabolism, or whether they are related to other factors such as poor general health, co-occurring medical conditions or neuromuscular impairments, or lifestyle behaviors. Recent research advances from studies focused on this issue include:

- A prospective population-based study followed bone mineral density changes in older men treated with different types of AEDs known as enzyme-inducing or non-enzyme inducing depending on their mechanism of action. In the study, men treated for epilepsy or other conditions with non-enzyme inducing AEDs (most commonly gabapentin) had more significant more bone loss when compared to controls [237]. In another study, decreased bone mineral density in adults treated with valproate, a non-enzyme inducing AED, did not correlate with length of treatment, suggesting valproate may not have long term effects on bone [238]. The study adds to contradictory findings about valproate's effects on bone, pointing to a need for well-designed prospective studies to address the question.

- Other research has begun to provide evidence into possible mechanisms for an effect of AEDs on bone metabolism. One study that looked at people and rats found that decreased bone mineral density and increased bone turnover after longterm phenytoin treatment was independent of vitamin D levels, suggesting alternative mechanisms to some previously proposed for the effects of AEDs on bone [239, 240].

E. Develop effective methods for diagnosis, treatment and prevention of non-epileptic seizures (NES).

Background:

Non-epileptic seizures (NES) are episodes that outwardly resemble epileptic seizures but that are not accompanied by aberrant neuronal activity characteristic of epilepsy. NES may have physiological or psychological origins, can occur in people with as well as without epilepsy, and may account for as many as 20% of referrals to epilepsy centers. Improved understanding and recognition of NES could inform better treatments and ways to reduce the burden and costs associated with diagnostic evaluation and ineffective and potentially harmful use of anticonvulsant drugs.

Summary of advances:

The differential and timely diagnosis of NES and epilepsy remains an important challenge to limiting the burden and cost of delaying appropriate treatment. Although research continues to confirm the value and importance of short and long-term monitoring with combined video and electroencephalography (VEEG) recordings of brain activity for NES diagnosis, recent studies have also highlighted the need for a multifaceted approach. Other efforts have focused on the underlying causes and risk factors for NES and on developing effective treatments.

- One study found only moderate inter-rater reliability of VEEG for NES diagnosis, underscoring the difficulty and subjective nature of NES diagnosis and the importance of integrating clinical history and physical exam findings with the results of VEEG [241]. A number of studies have begun to look at other factors that may differentiate between epileptic and non-epileptic seizures, such as linguistic analysis of patients' accounts of their seizures [242-244] or patterns of breathing and types of body movements [245]. Researchers have also developed and prospectively validated a 53-item self-administered questionnaire to screen for NES patients that inquires about sociodemographics, clinical and seizure-related information, and psychosocial variables [246].
- Much of the research literature concerning common susceptibility factors for and causes of NES focuses on demographics and the description of co-morbid psychiatric disorders in NES patients, with findings showing high rates of depression, anxiety, post-traumatic stress disorder (PTSD), dissociation, and other somatoform symptoms in which physical symptoms mimic disease or injury in the absence of an identifiable physical cause. Recent articles have underscored the heterogeneity of potential causes of NES and their comorbidities [247-252].
- A number of recent studies have added to the evidence that approaches based on cognitive behavioral therapy (CBT) and psychodynamic therapy may be effective treatments for NES. In trials and case reports, such approaches decreased the frequency of NES and also improved measures of depression, anxiety, somatic symptoms, quality of life, and overall psychosocial functioning [253-256]. Efforts are also underway to test pharmacological treatments for NES [257].
- Determining what is currently considered "treatment as usual" is an important step toward improving care for NES. Responses to the first known survey of national practices [258] showed that most American Epilepsy Society clinicians reported discussing the diagnosis of NES with patients, with 69% of neurologists continuing to follow patients after diagnosis. Antiepileptic drugs were tapered by 83% of the respondents, and 47% prescribed psychotropic medications if co-morbid psychiatric conditions were diagnosed.

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