Epilepsy Research Benchmarks

Progress Report
2007 – 2012

Epilepsy Research Benchmarks Progress Report, 2007 – 2012

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Preface

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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 in shifting and expanding the focus of epilepsy research beyond treating seizures and toward cures for epilepsy, 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 important research priorities moving forward and as a framework for periodically "benchmarking" progress. A second conference in 2007, "Curing Epilepsy: Translating Discoveries into Therapies," reassessed the state of epilepsy research and revised the Benchmarks, adding emphasis on the comorbidities of epilepsy and sudden unexpected death in epilepsy (SUDEP).

Today, over a decade since they were first developed, the Benchmarks have been increasingly embraced by the entire epilepsy community, including NIH, researchers, and epilepsy professional and advocacy organizations. NINDS looks to the Benchmarks when planning investments in epilepsy research, including the recently developed Centers without Walls program, Epilepsy EUREKA grants, and an initiative for translational research focused on the prevention of epileptogenesis and the treatment of drug-resistant epilepsy. Moreover, the American Epilepsy Society incorporates the Benchmarks into their Annual Meeting; the Benchmarks are cited in research articles, reviews, and grant applications; and Congress has also recognized Benchmarks priorities. Most importantly, epilepsy research has yielded exciting advances across all areas of the Benchmarks. The Epilepsy Benchmarks Stewards, including researchers who participated in the first Curing Epilepsy conference and newer investigators who have helped the Stewards group to grow, have worked over the years to track and promote this progress. In the reports that follow, the Stewards synthesize research advances related to each of the 2007 Epilepsy Research Benchmarks, and present their views on new and ongoing opportunities and challenges.

These reports demonstrate that research progress and refinements in our understanding of epilepsy can also point to new directions. Plans are well underway for a third conference, "Curing the Epilepsies 2013: Pathways Forward," a title that emphasizes the diversity of epilepsy types and conveys a sense of optimism toward finding cures. As the epilepsy community prepares to reconvene, we applaud the progress made toward meeting the Epilepsy Research Benchmarks to date, and we look forward to furthering our work together on shared priorities for the years to come.

Benchmarks Area I - Prevent epilepsy and its progression.
Perspectives on Progress from Area I Chairs

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Epilepsy comprises numerous distinct syndromes and underlying causes. Although specific types of epilepsy may have unique pathophysiological mechanisms, a broad hypothesis in this field is that convergent mechanisms of epileptogenesis may be shared by different forms of epilepsy. Animal models and clinical trials over the past two decades have repeatedly tested the hypothesis that the process of epileptogenesis involves the same mechanisms that are responsible for acute seizures in the epileptic brain. This hypothesis has been found wanting because antiseizure drugs have not prevented the development of epilepsy in humans at risk. Testing a prevention strategy is complicated by the diversity of epileptogenic mechanisms and by our inability to differentiate between mechanistic pathways in any given individual or group of individuals. Efforts in the last five years have been focused on a variety of alternative hypotheses, the most promising among them include interruption of mTOR signaling or inflammatory pathways, preservation of blood-brain barrier integrity, and neuromodulation. Workshops and funding initiatives involving AES, ILAE, NINDS and epilepsy advocacy organizations have helped to clarify definitions of epileptogenesis and antiepileptogenesis, deepened the discussion of appropriate animal models for different epilepsy syndromes, and made funding available to support exploratory collaborative research to evaluate the translational potential of disease modification or prevention therapy. Large-scale collaborations such as the Epilepsy Phenome/Genome Project and the NINDS Centers without Walls have been initiated both in the United States and abroad, and these offer the possibility of making significant advances in the discovery and validation of new antiepileptogenic strategies. Substantial advances in animal model development in recent years have improved understanding of the pathophysiology of specific acquired epilepsies including those due to viral encephalitis and cortical dysplasia, as well as infantile spasms.

A major challenge, and one of our most important opportunities, lies in unraveling the details of inflammatory and metabolic pathways that are specifically hijacked to reduce seizure threshold. The mTOR pathway has been shown to be critical for epileptogenesis in multiple mouse models of tuberous sclerosis complex (TSC, a genetic condition and cause of epilepsy), but recent animal studies also provide some evidence for a possible role of mTOR in epileptogenesis related to focal cortical dysplasia, status epilepticus-induced limbic epilepsy, traumatic brain injury, infantile spasms, and neonatal hypoxia. The antiepileptogenic effect of mTOR inhibitors is dependent on timing and duration of treatment. mTOR inhibitors have recently been approved for treating tumors in TSC patients and are currently being investigated in a clinical trial of epilepsy in TSC. Inflammatory mechanisms involving interleukin-1β (IL-1β) activation have similarly been found to be active in a variety of animal models and human brain specimens of different types of epilepsy. Interleukin-1β released mainly from activated glia, and toll-like receptor 4 engaged by a danger signal protein released from injured neurons, both converge on a signaling pathway that leads to the phosphorylation of the NR2B subunit and hence potentiation of NMDA receptors. Ifenprodil, a selective NR2B antagonist, prevents the proconvulsive effect of IL-1β in mouse models, which explains how one facet of inflammation lowers seizure threshold and thus might be pro-epileptogenic. An inhibitor of IL-1β synthesis is now being tested in a disease-modification trial of patients with intractable epilepsy. Recent studies have also advanced understanding of the connection between energy metabolism and neuronal excitability, and are contributing to a firmer mechanistic understanding of the ketogenic diet that involves regulation of mitochondrial energy metabolism and repression of a specific pro-epileptogenic transcriptional program.

Recognizing that our opportunity for prevention exists because of a months-to-years delay between brain insult and onset of spontaneous recurrent seizures, the epilepsy community is placing increased attention on the development of a set of valid biomarkers to measure and signal the stages of epileptogenesis. Promising biomarkers include alterations in hippocampal MRI images (early swelling, later shrinkage, signal changes as seen in the recent data from the FEBSTAT study), alterations in white matter tracts in specialized MRIs, the presence of interictal spikes and high frequency oscillations in the EEG, the presence of early seizures after the inciting event (as in TBI studies), and the appearance of a blood cytokine profile that would signal brain inflammation. There is need for a large prospective project that captures at-risk epilepsy patients in an on-going fashion for many years combined with long-term outcome measurements.

Area I Benchmarks Progress Summaries

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

B. Identify underlying mechanisms of epileptogenesis.

1. **Identify at least one susceptibility gene or other risk factor (e.g., viral, trauma, autoimmune) and identify how it predisposes to changes in network excitability.**

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Summary of key advances – epilepsy genetics

Key advances for these related benchmarks have been in epilepsy genetics. While the goal of understanding the complexities of the genetic underpinnings of epilepsy is far from being met, there has been substantial progress in this field. Discoveries have included the identification of single genes in individuals and families with epilepsy. This has been achieved using not only traditional techniques of linkage analysis and positional cloning but far more often next-generation sequencing, which has revolutionized the field and enhanced the speed with which discoveries are made. This has allowed the identification of new genes for established epilepsy syndromes and new syndromes for established epilepsy genes. In addition, there has been increasing recognition of a role for copy number variations in the development of and predisposition toward epilepsy.

Each individual discovery in epilepsy genetics has shed light on the larger picture of why epilepsy occurs. Together, they have changed our way of thinking about the potential for finding a cause for an individual's epilepsy. In the past, an individual with severe epilepsy with normal neuroimaging and normal screening metabolic evaluation was considered to have "idiopathic" epilepsy. Now, the progress in epilepsy genetics—modest though it may be in 2012—has led to the conceptualization of such cases as genetic until proven otherwise. The advances made thus far have already begun to influence clinical practice, where chromosome microarray analysis and sequencing of panels of epilepsy genes have become more widely available.

New or ongoing challenges and opportunities for research – epilepsy genetics

A major factor complicating the study of the causes of epilepsy, genetic and non-genetic, is the phenotypic and genetic heterogeneity of epilepsy. Just as autism has been shown to have several genetic causes, both inherited and *de novo*, we expect the same to be the case for epilepsy. Past studies, even those involving large numbers of patients, had not been successful in identifying genes through genome-wide association, in large part because the patients included were phenotypically heterogeneous and would thus be predicted to have a number of distinct causes and susceptibilities. Two major drivers of success in epilepsy genetics are the advent of next-generation sequencing and the recognition that collaborative efforts are needed to be able to study large groups of patients. Large-scale collaborations (such as the Epilepsy Phenome/Genome Project and the NINDS Center without Walls Epi4K Project) have been achieved both in the United States and abroad, and these offer the possibility of making significant advances in our understanding of the complex genetic basis of common forms of epilepsy, as well as the identification of additional gene mutations causing epileptic encephalopathies and malformations of cortical development.

As next-generation sequencing technologies are used, there is the on-going challenge of developing sophisticated analytical methods to accurately and efficiently identify candidate genes for epilepsy. As these new methods allow for increasingly rapid identification of candidate genes for epilepsy, a major challenge is to develop reliable and efficient validation and functional studies. This will be critical not only so that genetic diagnosis can be more widely implemented in the clinical arena, but also for addressing the challenge of translating genetic discoveries into the development of rational epilepsy treatment. Specifically, an unmet need in the field is high-throughput functional validation of genetic variants—both point mutations in single genes and copy number variants including several genes. High-throughput functional validation will require advances in a number of approaches, including *in silico* prediction tools and *in vitro/in vivo* demonstration of pathogenicity, both for individual and multiple genome variants. Coupled to this is the need for

new methods for high-throughput pre-clinical rational drug development in order to translate the discovery of pathogenic variants into effective therapies.

Summary of key advances – autoimmune-mediated epilepsy

In the past 5 years, there have been major advances in the identification of autoimmune, antibody-mediated epilepsy. These include the identification and increased recognition of causes for refractory epilepsies with aggressive onset, often with resultant clinical pictures resembling encephalitis (e.g., syndromes caused by antibodies targeting the NMDA receptor, GABA-B receptor, LGI1, and others). Even though these discoveries are relatively new, they have resulted in a change in clinical practice in that clinical testing for some of these antibodies is now available and becoming increasingly routine. More important, there are early retrospective clinical data suggesting that immune modulation can be effective in the treatment of these otherwise refractory and often devastating syndromes.

New or ongoing challenges and opportunities for research – autoimmune-mediated epilepsy

This is an exciting area that has been under-recognized and that clearly warrants further investigation. Three major challenges and goals in the field of autoimmune-mediated epilepsy are (1) to identify additional causes, both paraneoplastic and non-cancer-related, and to make testing for them widely available to clinicians; (2) to increase awareness in the clinical community about these potentially treatable causes of epilepsy; and (3) to translate these scientific discoveries into specific, effective treatments for each antibody-mediated syndrome.

B. Identify underlying mechanisms of epileptogenesis.

2. Identify at least one epileptogenic mechanism that is reversible, or has influence at critical developmental times.

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Summary of key advances

The developing brain is highly susceptible to seizures in response to neurological injury as well as to the process of epileptogenesis following a precipitating insult. Up to 25% of neonates experiencing seizures develop epilepsy later in life. Identifying the factors that affect seizure and epilepsy susceptibility will advance our understanding of developmental brain function and provide the opportunity to intervene and retard or abort the process of epileptogenesis. Two advances are highlighted:

Depolarizing action of GABA:

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian central nervous system. In the mature nervous system, GABA produces inhibition by binding to its specific postsynaptic receptor (GABA-A). In the developing brain, GABA produces excitation rather than inhibition, due to differential development of chloride ion transporters KCC2 and NKCC1. The switch from GABA's depolarizing action to its hyperpolarizing action is related to the relative balance in the expression of these two transporters. The early-life depolarizing action of GABA has an important trophic role but also contributes to the increased susceptibility of the immature brain to seizure generation and to the notoriously poor efficacy of GABAergic agonists (barbiturates, benzodiazepines) as anticonvulsants for neonatal seizures. In the period 2007-2012, considerable progress has been made in elucidating the characteristics and consequences of the depolarizing role of GABA, including:

- Potential role of bumetanide, an NKCC1 inhibitor, as an age-specific therapy for neonatal seizures.
- Synergistic effects of bumetanide and phenobarbital in neonatal seizures in rodents, suggesting an age-specific, rational polytherapy. Data have also accumulated on certain time windows during which this effect is seen.
- Gender-specific developmental profiles in the depolarizing actions of GABA.
- Depolarizing actions of GABA in epilepsies beyond the neonatal period, including temporal lobe epilepsy and epilepsy arising from cortical malformations.

Together, evidence is emerging across many epileptic disorders that perturbed GABAergic signaling due to altered chloride balance may determine relative excitability in epileptic tissue. These findings suggest a potential role for novel epilepsy therapies at multiple ages.

Hypoxic-ischemic encephalopathy (HIE):

HIE is the most frequent cause of neonatal seizures and subsequent epilepsy, though the exact risk factors and extent of post-hypoxic ischemic epileptogenesis remain to be determined. In the period 2007-2012, progress in elucidating the mechanisms and treatment of HIE seizures includes:

- Numerous strategies have been tested to reduce neonatal hypoxia-ischemia related brain damage and subsequent epilepsy, including GABA receptor blockers (phenobarbital), broad-spectrum anticonvulsants (lamotrigine), erythropoietin, matrix metalloproteinases, AMPA receptor blockers (topiramate, talampanel), and hypothermia (therapeutic cooling).
- Combinations of above therapies (e.g., phenobarbital plus therapeutic cooling) might have additional benefits.
- Role of unblocking "silent" NMDA receptors in neonatal seizures.
- Structural modifications following HIE seizures that predispose to epilepsy and cognitive impairment.

Together, these animal studies explore critical aspects of neonatal brain circuitry and function that could lead to seizures and methods to intervene to prevent epileptogenesis.

Factors promoting or hindering progress

- Progress has been enhanced by the realization of the clinical need and application of translational approaches to both of the above mechanisms.
- Progress is hindered by the inherent multiplicity of potential mechanisms mediating seizure generation and neuroplastic changes in the developing brain, leading, at times, to somewhat erratic and unfocused approaches to therapy.
- Uncertainties in how seizures are defined in the immature brain (e.g., What is a seizure at this age, electrographically and clinically, and does this change over time?).
- Methodological issues in research on the immature brain (e.g., reliable electroencephalographic recordings from such small brains and seizure phenotype uncertainties).
- Difficulties in recruiting sufficient numbers of infants for clinical trials.

New or ongoing challenges and opportunities for research

- As above, clinical trials of novel compounds and combinations thereof.
- Improved technology with regard to electrophysiological analysis of the immature brain.

B. Identify underlying mechanisms of epileptogenesis.

3. Identify at least one specific role for non-neural mechanisms (e.g., glia, immune cells, angiogenesis) in epileptogenesis.

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Summary of key advances

Astrocytosis is a common pathologic finding in epileptogenic tissue. Although the physiologic mechanisms by which astrocytes contribute to epileptogenesis are not fully described, recent data from human specimens as well as from animal focal epilepsy models provide important insight. For instance, translational experiments demonstrate that mouse CA1 neurons proximal to areas of enhanced astrocyte proliferation have reduced inhibitory but not excitatory synaptic currents. These data suggest that astrocytosis may interfere with local inhibitory mechanisms. Yet another role for astroglia in epileptogenesis is suggested by patch clamp recording with simultaneous calcium imaging in a rat entorhinal cortex seizure model. These data demonstrate that astrocyte intracellular calcium elevation correlates with both the initial development and the maintenance of focal epileptiform activity, and suggest that neuron-astrocyte interaction may be a critical component of local epileptogenic microcircuitry.

Perhaps of more immediate translational relevance, results from a number of studies suggest that compromised astrocyte glutamate transport contributes to epileptogenesis. Excess increase in extracellular glutamate appears to contribute to epileptogenesis after a number of brain insults including status epilepticus and traumatic brain injury (TBI). Genetically determined defects in astroglial glutamate transport also reliably lead to seizures. Clearance of extracellular glutamate is mediated largely by astrocyte glutamate transporters (excitatory amino acid transporters 1 and 2; EAAT-1 and EAAT-2) whose expression is reduced in the hippocampus of patients with temporal lobe epilepsy, in epileptogenic human cortical dysplasia specimens, and also after traumatic brain injury in humans. Since EAAT expression in human astrocytes may be upregulated by β-lactam antibiotics, particularly by ceftriaxone (which has excellent blood-brain barrier penetrance), these data suggest prospects for therapeutic intervention aimed to mitigate glutamate-mediated neuronal injury and epileptogenesis after brain injury. Such therapeutic plausibility is supported by recent data in a mouse tuberous sclerosis model showing that expression of astrocyte glutamate transporter 1 (GLT-1; rodent analog of EAAT-2) was depressed at baseline, and enhancement of its expression by ceftriaxone reduced seizure frequency, reduced neuronal loss and improved survival in the TSC mice.

Recent data also implicate an epileptogenic effect of reactive and defective astroglia as occurs in glial tumors where epilepsy is a frequent co-morbidity. Here too, the data suggest that seizures result from glutamate locally released by the tumor cells. Furthermore, a recent study identifies an FDA-approved drug, sulfasalazine, a x_c^- cysteine-glutamate transporter inhibitor, as a potential therapeutic.

Factors promoting or hindering progress

Beyond epilepsy, the roles of astrocytes in neural function is an active topic of investigation in neuroscience, and with improved understanding of basic astrocyte function, the understanding of the astrocyte's role in epileptogensis is certain to improve. However, clinical translation of the basic data to human therapeutic trials is lacking. But the relatively favorable safety profile of ceftriaxone suggests that near-future clinical trials are realistic.

New or ongoing challenges and opportunities for research

The prevalence of astrocytosis in excised human epileptogenic tissue, particularly in cases of temporal lobe epilepsy, has provided the opportunity to study its role in epilepsy for decades. More recently, the capacity to study human postoperative tissue *in vitro* by electrophysiological techniques seems likely to enable further insight into astrocyte-neuron interactions. As with much basic neuroscience, translation of the data to human clinical applications remains a major challenge and an unmet need. However, as above, the contribution of astrocyte glutamate transport to epilepsy may be explored in clinical trials in the near future.

B. Identify underlying mechanisms of epileptogenesis.

4. Identify at least one neuronal mechanism in microcircuits that contributes to epileptogenesis.

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Summary of key advances

There has been major progress in advancing our understanding of the neuronal mechanisms in microcircuits that contribute the development of epilepsy.

GABAergic transmission defects in epilepsy:

It is now well established that abnormalities in GABAergic synaptic transmission can promote epilepsy with defects occurring at multiple levels. A few examples include: 1) reduced intrinsic excitability due to reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy; 2) human epilepsy due to mutations in $GABA_A$ receptor subunit genes (GABRs) GABRA1, GABRB3, and GABRG2; and 3) reduced GABAergic basket cell inhibition in models of acquired epilepsy.

Persistent glutamatergic circuit immaturity in genetic form of human epilepsy:

Recent studies have now also implicated defective pruning and persistent immaturity of glutamatergic synapses in a human genetic form of epilepsy that involves mutations in LGI1.

Signaling pathways that promote epileptogenesis:

Studies have built strong evidence that activity in the mTOR and AKT and TrkB signaling pathways promotes epileptogenesis. Further support for disturbances in these pathways as a driver of epilepsy comes from recent genetic studies identifying somatic mutations that activate mTOR and AKT signaling. These mutations were associated with hemimegalencephaly, an often drug-refractory epilepsy disorder associated with abnormal cortical tissue containing excess numbers of aberrant neurons and glial cells. While hemimegalencephaly is commonly treated by surgical removal of the affected cortical hemisphere, it is possible that ongoing activity in these signaling pathways promotes the epileptiform discharges emanating from the abnormal regions, as suggested by the responses of tuberous sclerosis models to rapamycin.

Mapping of microcircuits in human epileptic brain tissues in vitro and in vivo:

Extracellular recordings of units were performed across the distributed circuitries of the human medial temporal lobe resection specimens. The location of emergent discharges most consistently occurred in the subiculum. By examining the extracellular spike properties, the discharges were attributed to the firing of pyramidal (glutamatergic) neurons. *In vivo* recordings from epilepsy patients also supported this mapping of the pre-ictal discharge locus.

In another example of studies of human epilepsy but in this case all *in vivo* and examining both medial temporal and frontal cortical, this group found heterogeneity in the pre-ictal and ictal firing of large populations of neurons in some cases near and other times recorded more remotely from the seizure initiation zone. One of the more interesting features was a relatively synchronous shut-down of the population of neurons. Although the precise mechanism was not defined, it is a valuable assay of network wide anti-epileptic mechanisms in humans *in vivo*. One can readily imagine that this group is now well poised for local pharmacological interventions to assess potential mechanisms (e.g., adenosine, decreased extracellular pH).

Epilepsy in brain tumors:

Epilepsy is a frequent comorbidity in individuals with glial brain tumors and was the presenting symptom for the late Senator Edward Kennedy. A recent study supported the notion that seizures results from glutamate locally released by the tumor cells. It further identified an FDA-approved drug, sulfasalazine, a xc- cystine-glutamate transporter inhibitor, as a potential therapeutic.

Factors promoting or hindering progress

Ongoing support of epilepsy research has been a critical factor in promoting progress. Newly developed *in vivo* molecular and genetic technologies have strongly facilitated progress in epilepsy research, and in many cases these newer technologies are just beginning to be utilized. These methods capitalize on cell-type specific and inducible gene manipulations in mice utilizing Cre/loxP, FLP/FRT, and tTA/teto technologies used either in transgenic/knock-in mice or through steriotaxic injections of viral vectors (e.g., AAV). Cell-type specific fluorescent tagging helps to reliably identify a specific neuronal subtype within a complex neuronal circuit, like cortex, allowing these neurons to be studied further, such as by brain slice patch clamp electrophysiology or *in vivo* imaging. Technologies for exciting and inhibiting neurons *in vivo* and *in vitro* (brain slices) using light-activated channelrhodopsin and halorhodopsin and designer receptors exclusively activated by designer drugs (DREADDs) are just beginning to be used in epilepsy research to map circuits that can drive or prevent seizures. Methods are also available to monitor large populations of neurons simultaneously using genetically encoded calcium (GCaMP) or chloride (Clomeleon) indicators.

New or ongoing challenges and opportunities for research

A new technology involving an implantable imaging device enables the monitoring of fluorescence signals from large populations of neurons across broad areas in freely moving mice. Other technologic advances permit imaging from structures deep in the brain. More recent studies have also advanced methods to perform global analysis of the brain using serial two-photon microscopy and newer methods of making the brain transparent followed by fluorescence light sheet microscopy. These methods may also be combined with methods for monitoring detailed structural features of specific neurons and with neuronal activity fluorescent reporter mice (c-fos or Arc). With these newer technologies, we are likely to see research on epilepsy expand beyond the traditional focus on cortical and hippocampal areas.

B. Identify underlying mechanisms of epileptogenesis.

5. Identify convergent pathways or mechanisms of epileptogenesis in multiple models and human epilepsy syndromes.

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Summary of key advances

Epilepsy is not a single disease, but comprises numerous, distinct syndromes and underlying causes. Although specific types of epilepsy may have unique pathophysiological mechanisms, there are also general principles and mechanisms of epileptogenesis that may be shared by different forms of epilepsy. Identifying convergent pathways or mechanisms of epileptogenesis among a variety of epilepsies will more quickly and efficiently advance knowledge in the field as a whole and, from a therapeutic standpoint, will promote development of novel targeted treatments that have widespread applicability to a larger proportion of patients with epilepsy. Over the past five years, significant progress has been made towards achieving this goal. Numerous biological pathways or mechanisms have been identified as potential candidates mediating epileptogenesis in multiple types of seizures/epilepsy syndromes. Besides identifying additional converging mechanisms of epileptogenesis, unmet goals to be addressed in the future are to prove more definitively that these candidate mechanisms are indeed casually involved in epileptogenesis in the various epilepsy types and to translate these findings into actual clinical trials of antiepileptogenic therapies.

Candidate mechanisms of epileptogenesis that have been identified and studied in multiple epilepsy models and syndromes over the past 5 years span a wide variety of biological processes, such as molecular genetic mechanisms (e.g., transcription, translation, epigenetics), cell signaling pathways (e.g., mammalian target of rapamycin [mTOR], mitogen-activated protein kinase [MAP kinase]), channels/receptors/transporters mediating neuronal excitability (e.g., sodium channels, GABA receptors, NKCC1 transporters), specific cell types (e.g., glia), brain inflammation, and vascular/blood-brain barrier mechanisms. Among this growing list, two examples are particularly well-developed and poised to translate into potential therapeutic applications: (1) the mTOR pathway, and (2) inflammatory mechanisms.

The mTOR pathway has been most definitively shown to be critical for epileptogenesis in multiple mouse models of tuberous sclerosis complex (TSC, a genetic condition and cause of epilepsy), but recent animal studies also provide some evidence for a possible role of mTOR in epileptogenesis related to focal cortical dysplasia, status epilepticus-induced limbic epilepsy, traumatic brain injury, infantile spasms, and neonatal hypoxia. mTOR inhibitors have recently been approved for treating tumors in TSC patients and are currently being investigated in a clinical trial of epilepsy in TSC. Inflammatory mechanisms, such as cytokine interleukin-1β (IL-1β) activation, have similarly been found to be active in a variety of animal models and human brain specimens of different types of epilepsy. As a result, a specific IL-1β inhibitor is also being tested in clinical trials of patients with intractable epilepsy.

Factors promoting or hindering progress

The ability to identify convergent mechanisms of epileptogenesis among different types and models of epilepsy has been promoted by several key factors.

- Perhaps most importantly, a large expansion in the number and availability of animal models for different types of epilepsy have allowed epileptogenic mechanisms to be identified and compared between different models, such as in TSC, other genetic epilepsies, and infantile spasms.
- The increasing use of video-EEG in animal research has also improved the yield and accuracy of documenting epilepsy in different mechanism-based models, especially in models that were created for other reasons and might not have originally been suspected as having epilepsy.
- Finally, heightened awareness and communication among and between basic scientists and clinical researchers about the importance of identifying convergent mechanisms of epileptogenesis has been a consistent theme in

recent research meetings and workshops, such as the American Epilepsy Society annual meetings and the **NINDS Workshop on Antiepileptogenesis and Disease Modification.**

New or ongoing challenges and opportunities for research

Although much progress has been made in identifying candidate mechanisms of epileptogenesis in multiple types of epilepsy, there have been limitations in this area, which will remain a challenge for future research.

- Despite the growing list of candidate mechanisms, very few have been rigorously proven to be necessary for epileptogenesis in any given epilepsy model or syndrome. In many cases, there are correlative data that a biological mechanism or process is deficient, dysregulated, or abnormally active in animal models, but definitive proof of causation is still lacking. Thus, better pharmacological, genetic, or other methods and study designs need to be employed to provide authoritative evidence that a specific mechanism causes epileptogenesis first in one, and then multiple, models of epilepsy.
- Even in cases where evidence for a causal role is strong (e.g., mTOR in TSC), there is still a significant lag in translating basic science findings to clinical trials, especially related to antiepileptogenesis. For example, while mTOR inhibitors have been approved for treating tumors in TSC patients, there is currently only one phase 2 trial of an mTOR inhibitor for epilepsy in TSC. Furthermore, this trial uses the standard paradigm of treating intractable epilepsy, which may not take full advantage of the antiepileptogenic potential of mTOR inhibitors in TSC.
- While there have been multiple discussions on how to best design a true antiepileptogenic clinical drug trial, practical, ethical, and regulatory factors seem to have hindered progression at this point.

Thus, significant challenges still exist on both the basic science and clinical levels in demonstrating and exploiting findings on convergent mechanisms of epileptogenesis.

B. Identify underlying mechanisms of epileptogenesis.

6. Identify the underlying cellular and molecular properties that are associated with electrophysiological and functional abnormalities.
7. Identify homeostatic mechanisms that prevent spread of microsynchrony.

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Summary of key advances

Substantial progress has been made during the past five years that links specific inflammatory and metabolic pathways to ion channel and network properties that in turn promote hyperexcitability. These advances contribute to a growing realization that some inflammatory molecules and energy metabolites play dual roles to control the activity of neuronal networks.

- A pro-inflammatory signaling pathway has been identified that promotes seizures by potentiating NMDA receptor activation. Interleukin-1β (IL-1β) released mainly from activated glia, and toll-like receptor 4 engaged by a danger signal protein released from injured neurons, both converge on a signaling pathway involving sphingomyelinase and Src-family kinases, which leads to the phosphorylation of the NR2B subunit and hence potentiation of NMDA receptors. Ifenprodil, a selective NR2B antagonist, prevents the proconvulsive effect of IL-1β, which explains how one facet of inflammation promotes seizures.
- Prolonged seizures accompanied by hypertension are known to cause spotty breakdown of the blood brain barrier. It is now recognized that extravasation into the brain parenchyma of plasma proteins, prominent among which is albumin itself, activates a TGF-β pathway that promotes hyperactivity of neurons in the zone of blood-brain barrier breakdown. Moreover, interactions between leukocytes and vascular endothelial cells that result in leukocyte infiltration into injured brain regions contribute to epileptogenesis in a pilocarpine rodent model of epilepsy.
- Astrocytes have long been known to have non-overlapping spatial domains that create microdomains within the brain. This strict domain organization has now been shown to break down in the chronic epileptic brain, such that the spatial extent of astrocyte-astrocyte touching is increased. The breakdown of astrocyte network structure could widen the volume of tissue that is involved in microsynchrony beyond that of a single astrocyte.
- Recent studies have begun to unravel the connection between energy metabolism and neuronal excitability, and in the process are contributing to a firmer mechanistic understanding of the ketogenic diet. A manipulation as complex as diet is likely to engage multiple mechanisms. Accordingly, two means of seizure control have now been identified.
    - The first involves a mitochondrial protein, Bcl-2-associated Agonist of Cell Death (BAD), formerly discovered to promote apoptosis but now shown to regulate mitochondrial energy metabolism. In neurons, inactivation of BAD results in preferential usage of ketone bodies over glucose and this correlates with resistance to kainic acid or PTZ induced seizures. It is thought that the beneficial effects of BAD inactivation work through increasing the open probability of K_{ATP} channels. Given that upstream growth factor pathways control BAD activity via phosphorylation, the discovery that BAD controls seizure propensity suggests that this key regulator of mitochondrial energy metabolism could be a therapeutic target.
    - The second relates a by-product of glycolysis to transcriptional control of kindling progression by the repressor REST. Decreased glucose utilization in the presence of the glycolytic inhibitor 2-deoxy-D-glucose (2DG) results in reduced levels of the glycolytic intermediate, NADH. NADH is an allosteric modulator of the nuclear protein CtBP, an obligate corepressor for the transcription factor REST. Thus high levels of glycolytic NADH bind CtBP and prevent CtBP interacting with REST resulting in heightened expression of pro-epileptic genes. Reduction of NADH levels with 2DG allows CtBP binding to REST, repression of a pro-epileptogenic transcriptional program and retardation of kindling.

New or ongoing challenges and opportunities for research

- The recent introduction of a number of techniques developed mostly outside the epilepsy field has allowed new approaches to classical questions of seizure control. These techniques allow one to ablate specific populations of leukocytes, to image metabolic intermediates, and to identify genes associated with specific chromatin modifications.
- Both energy metabolism and inflammation employ multiple pathways. A major challenge, and one of our most important opportunities, lies in unraveling the details of inflammatory and metabolic pathways that are specifically hijacked to control excessive and synchronous neuronal activity.

C. Identify biomarkers for epileptogenesis.

1. **Identify and validate one biomarker to predict progressive or intractable epilepsy in new-onset patients.**
2. **Identify and validate one biomarker (e.g., imaging, electroencephalographic (EEG), blood test) to predict development of epilepsy in at-risk individuals (human or animal).**

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Summary of key advances – predicting intractable epilepsy or disease progression

Unfortunately, there is still no known method for preventing the "worsening" of epilepsy in those who already demonstrate spontaneous recurrent seizures. In fact, the question of whether epilepsy actually progresses in severity once it is established remains somewhat controversial. Evidence from long term follow-up with imaging and cognitive studies demonstrates that some patients with specific forms of epilepsy have slowly progressive deterioration, but clearly many patients do not demonstrate this and whether these changes are also reflected in the character of their epileptic syndromes seems less clear even in those with progressive lesions. Some argue that patients may present with "controllable" seizures early only to have these become refractory after a period of time, a phenomenon possibly linked to the epileptogenic process itself. Others question the data and suggest that, even if true in some cases, the underlying neurobiological processes may be different between progression of the epileptic state and the changes that drive a normal brain to become permanently hyperexcitable. Of interest, there are almost no data that focus on this issue in either the basic science or clinical literature. The major surge in investigations into epileptogenesis focuses almost entirely on the development of epilepsy rather than progression.

Perhaps one relevant research finding relates to a series of clinical studies with new onset epilepsy patients carried out by Drs. Martin Brody, Patrick Kwan and colleagues that seems to emphasize that patients may be fall into two broad groups – one group (about 60% of adult new onset patients) appears likely to achieve seizure control with one or possibly two of the currently available antiepileptic drugs, and a second group which only occasionally become seizure free on any medication regimen. There are little data in these studies that indicate a progression in the patients' epilepsies, although this was not a primary focus of the research. These data support conclusions from earlier studies on whether treating a first seizure with anti-seizure drugs affects the likelihood of becoming refractory over time. In each of these studies, it appears that patients may be "refractory" when first seen by physicians, presumably after one, two or only a few seizures, but there is no current method for determining who will respond to treatment readily and who will be refractory. Thus, there seems to be little evidence that epilepsy is progressive in these patient populations.

Summary of key advances – predicting the development of epilepsy in those at risk

Although numerous etiologies can be responsible for causing epilepsy, an opportunity for prevention exists because of a delay between an inciting brain insult and the onset of spontaneous recurrent seizures (epilepsy). In most human epilepsy cases, this period of epileptogenesis ranges from months to years. It is in this window that identification of surrogate measures or biomarkers of epileptogenesis could allow intervention and monitoring of therapy to prevent or mitigate development of epilepsy in at-risk individuals. At the moment, there is no known mechanism for preventing the development of epilepsy after any inciting lesion, such as traumatic brain injury (TBI), status epilepticus, meningitis, stroke, etc. However, interest in identifying biomarkers for epileptogenesis has grown, and there is a lot more ongoing research, both in animal models and human patients, than just a few short years ago.

To date, there have been a number of changes in brain anatomy and physiology that are known to be associated with the epileptogenic process. These changes in human patients include alterations in hippocampal MRI images (early swelling, later shrinkage, signal changes as seen in recent data from the FEBSTAT study – a study of the effects of prolonged febrile seizures), alterations in white matter tracts, the presence of interictal spikes and high frequency oscillations in EEG recordings, and in some situations, the presence of early seizures after the inciting event (as in TBI studies). All of these events, however, can be seen in patients with similar risks who do not develop clinically identified seizures, and it is also not clear whether they contribute to progressive worsening. Moreover, as discussed below, clinical research in this area faces a number of challenges, including the reliance on clinical and EEG indicators of seizures – which may miss some nonconvulsive seizures. There has been more progress studying animal models of epileptogenesis. In this paradigm, the inciting event can be relatively carefully controlled and the subjects can be monitored with intracranial recordings at high bandwidths for days, weeks, and even months. Similarly, brain tissue can be examined morphologically and biochemically during the process. Despite these advantages, clear biomarkers for the process of epileptogenesis have not yet been identified.

Putative biomarkers of epileptogenesis for study in animal models and human studies may be identified within existing and developing methodologies such as electroencephalography (EEG), neuroimaging (functional and structural), and cerebral spinal fluid (CSF) or serological measures. Since 2007 no single definite biomarker for epileptogenesis has been identified and validated. Two experimental animal model studies, however, reveal promise for specific quantitative EEG and magnetic resonance imaging (MRI) techniques. First, one partially negative study for MRI and EEG as biomarkers in a febrile status epilepticus (SE) model that focused on the severity of initial insult (duration of seizure activity) found that chronically elevated interleukin-1β was only present in those animals that developed spontaneous seizures. As a possible answer to the negative prediction of EEG in this study were results from a separate study using a kainate-induced SE model and prolonged video EEG recording that revealed specific temporal features of EEG epileptiform abnormalities were indeed strongly correlated with subsequent epilepsy. These features—frequency and temporal clustering of EEG spikes—could only be detected with long-term monitoring. Also in contrast to the above mentioned partially negative study is an MRI based study in a fluid percussion model of post-traumatic epilepsy. Two independent experiments revealed that quantitative diffusion weighted MRI (the apparent average diffusion constant) in the hippocampus ipsilateral to the percussion injury was consistently associated with consequent development of decreased seizure threshold. Further, this diffusion abnormality was specifically correlated with degree of hippocampal mossy fiber sprouting, a classic finding of altered neuronal circuitry in human mesial temporal lobe epilepsy. Most compelling was that the MRI measure of hippocampal diffusion change was progressive, detectable acutely and subacutely, such that it may be extrapolated to suggest a relatively large diagnostic time window for detection and intervention.

New or ongoing challenges and opportunities for research

The identification of reliable biomarkers for the development of epilepsy after any of many possible risk factors or the progression of epilepsy after it is established is certainly one of the more critical areas in need of significant research advances in the epilepsy field. There are relatively little data available on determining which anatomical and physiological changes are only seen in individuals (or individual experimental animals) that develop epilepsy, as compared to those with similar risks who do not. Even less evidence exists regarding whether progression of these changes continues after the epileptic state has been established and whether they contribute to a worsening of the syndrome. There do not appear to be any studies in either the experimental or clinical literature focused on methods to prevent longer term anatomical or physiological changes in the brains of either animals or human patients with epilepsy. Similarly, there is little in the experimental literature connecting any progressive lesion with a worsening of the epilepsy.

A number of factors have hindered progress and may continue to be challenges. In terms of human (clinical) research, it is critical to recognize that almost all that is known is based on clinically identified seizures and that, in general, this is likely to be a significant underestimate of the true epidemiology. A variety of non-convulsive seizures may not be recognized by all but the most experienced and sensitive investigator, and many electrographic seizures may not produce changes in scalp EEGs or produce any clinically identified behavioral changes, yet they can be noted with intracranial recordings. Furthermore, with the exception of a few patients that have chronically implanted intracranial recording electrodes that are being monitored continuously, we have very little understanding of the underlying electrophysiology of either the normal or damaged human brain.

Another limitation has been that no well-defined cohort studies of at-risk epilepsy populations exist that may be exploited to identify epileptogenesis biomarkers. These kinds of studies are very long, require large populations and repeated measures (including multimodal measures such as MRIs and EEGs), require extensive age and health-matched controls, are not associated with any benefit for the participants, and are extremely difficult to get funded. However, such a project would not only aid biomarker discovery, but also would allow translational study of epileptogenesis mechanisms and related genetic susceptibility factors in human epilepsy. Finally, a continuously enrolling cohort would provide appropriate subjects for testing intervention and monitoring of treatment effects based on validated biomarkers. On the basic science side, once epileptogenesis reached the collective consciousness of the epilepsy field, the "holy grail" focused on preventing epilepsy in the first place and not on limiting its progression, if, in fact, it did progress. This kind of research would also require very long (and expensive) experiments, complex measures, the use of chronic drug administration, if the experiments were to mimic the human situation, and would also be very difficult to fund.

It is clear that prevention of epilepsy would be preferable to the current situation, in which treatment is only designed to target the symptoms of epilepsy once they are established. It is conceivable that a prevention strategy could be developed that is so benign (such as a vaccine) it could be applied to everyone at risk to prevent a fraction of those from developing epilepsy; but at present, this is not feasible. A more realistic prevention strategy would be one that is directed to only people who were clearly destined to develop epilepsy, once it is possible to identify them.

D. Identify approaches to prevent epilepsy or its progression.

1. **Identify at least one homeostatic mechanism that protects against the development of epilepsy or its progression.**
2. **Identify interventions that prevent, interrupt or reverse the epileptogenic process.**

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Summary of key advances

During the past five years, workshops and funding initiatives involving AES, ILAE, NINDS and epilepsy advocacy organizations have helped to clarify definitions of epileptogenesis and antiepileptogenesis, focused on optimizing approaches in preventing epilepsy and emphasized several translation models as high priority (e.g. status epilepticus, TBI, neonatal hypoxia, TSC, stroke, focal cortical dysplasia), and made funding available to support exploratory collaborative research to evaluate the translational potential of disease modification or prevention therapy in an epilepsy syndrome. In addition to these efforts, there have been several notable advances from basic research, although results have not yet met the short- or long-term goals associated with Benchmark 1.D.

Basic research in animal models of acquired epilepsy has identified potential targets for antiepileptogenic interventions (e.g. cell loss, morphological alterations, inflammation, blood brain barrier, neurogenesis, astrogliosis and angiogenesis), and new models have been generated that reflect important features of MTLE, infantile spasms and TSC. Preclinical animal studies on the mammalian target of rapamycin pathway found rapamycin treatment has antiepileptogenic effects (e.g. reduced epileptiform activity, reversed or prevented hippocampal and cortical structural alterations, reduced behavioral impairments) in TSC mice, and some status epilepticus models like kainic acid-treated, but not pilocarpine-treated, epileptic rodents. Treatment studies targeting brain inflammatory (e.g. IL-1 and TOLL-like receptors) or neurotrophic factor-mediated pathways (e.g. FGF-2, BDNF) have observed seizure reducing effects in acquired post-status epilepticus and kindling models.

New or ongoing challenges and opportunities for research

Factors that have hindered progress include a limited understanding of the specific mechanisms of epileptogenesis that are likely different for each of the many conditions that lead to the development of spontaneous seizures. Genetic background could presumably influence predisposition for epileptogenesis and epileptogenicity and is also a confounding factor. Long-term monitoring presents practical challenges for accurately determining the spatial and temporal properties of epileptogenesis and efficacy of antiepileptogenic interventions. Biomarkers of epileptogenesis are needed to identify the development of epilepsy and measure its progression and biomarkers of epileptogenicity to measure the presence of epilepsy and its severity. The latter would greatly facilitate basic research studies and are critical for purposes of clinical trials to identify patients who are at greatest risk for developing epilepsy and to accurately document prevention of epilepsy or cure.

E. Develop new animal models to study epileptogenesis.

1. Develop at least one new animal model of the development and progression of epilepsy.

H. Steve White, Ph.D.
University of Utah

Summary of key advances

Since 2007 considerable progress has been made in the development and utilization of new animal models that mimic the development of human epilepsy. Today, some of these new animal models of ictogenesis and epilepsy represent an important tool for elucidating the underlying mechanisms of seizures and epileptogenesis. They also have the potential to provide insight into the validity of various biomarkers of epileptogenesis. Further, many of the evolving animal models are beginning to show an important utility in the search for novel therapeutics for the symptomatic treatment and prevention of epilepsy.

Over the last five years, it has become ever clear that the heterogeneity of the various epilepsies is not likely to be modeled by any one model system, and thus efforts have been aimed at identifying etiologically appropriate animal models that display phenotypic, electrographic, and developmental features consistent with the human condition for which it is proposed to emulate. Thus, the need for multiple, syndrome specific models is obvious and immediate.

To this end, there have been several substantial advances in animal model development in recent years that have advanced a greater understanding of the pathophysiology of specific acquired epilepsies including viral encephalitis, cortical dysplasia, and infantile spasms. Further, substantial efforts have been made to further characterize many of the existing models of acquired and genetic epilepsy. For example, viral encephalitis is often associated with highly refractory epilepsy and substantial comorbidity. Previous attempts to model viral encephalitis in rodents have been hindered by poor long-term survival following inoculation with various viruses including human herpes virus type-6, influenza viruses, rotavirus, adenovirus, respiratory syncytial virus, and picornaviruses. In contrast, Theiler's murine encephalomyelitis virus, when injected into the cortex of C57 mice, precipitates an acute cytokine storm that is associated with acute symptomatic seizures within a few days of infection, acute and chronic hyperexcitability, and ultimately epilepsy in a large fraction of infected mice.

In addition, the development of an animal model of Tuberous sclerosis complex (TSC) in recent years has been providing important insight into the pathophysiology of TSC and other cortical dysplasias at multiple levels and has provided a platform to evaluate emerging therapies that target the underlying molecular mechanisms found to contribute to TSC; i.e., mammalian target of rapamycin (mTOR). Altered mTOR signaling is thought to contribute to epileptogenesis associated with other FCMs including focal cortical dysplasia, ganglioglioma, and hemimegalencephaly.

Factors promoting or hindering progress

Importantly, there has been an increase in appreciation of the value that a well-characterized model system can provide towards advancing knowledge of the disease process and bringing a new therapy to the clinic. The advances in model development that has taken place in recent years is in large part due to concerted efforts to 'back translate' molecular, genetic, phenotypic, and electrophysiological observations at the human level to the animal. Improved access to the necessary tools (e.g., genetic knock-in and knock-out approaches and rodent video-EEG monitoring) has certainly led to the creation and characterization of several etiologically specific model systems, including viral encephalopathy, TSC, and FCM. Nonetheless, progress is hindered by some of the same things that made it possible. For example, video-EEG is still often conducted using a tethered system which can lead to the loss of data when an animal prematurely loses its head cap assembly. This is particularly problematic when attempting to follow the progression of epilepsy after a given brain insult. Further, whether using a tethered or telemetry system to collect EEG data, the amount of data that can be generated from a chronic study can be overwhelming for most laboratories. Moreover, the resources necessary for creating, maintaining, and evaluating a model system can stretch research budgets.

New or ongoing challenges and opportunities for research

The problem with any non-human model of epilepsy is just that: it is a non-human model, and clinical validation may never be possible. This, however, should not discourage the continued characterization of a new model at all levels

(e.g., phenotypic, electrophysiological, molecular, genetic, pharmacological, etc.). For this to happen, the clinical and basic sciences have to continue to come together in a collaborative manner to share information and resources. Because of the heterogeneity of the epilepsies at the genetic and pathophysiological level, the number of models that could be developed is extremely high, and given the resources required to 'fully' characterize a new model, resources will likely be stretched even further. A model system that mimics the development or progression of epilepsy has the potential to be used for the identification of a disease modifying or antiepileptogenic therapy. However, the challenge will be determining when the data are strong enough to support moving that therapy forward to the clinic.

E. Develop new animal models to study epileptogenesis.

2. Develop at least one new animal model of the epileptic encephalopathies of infancy and childhood.

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Summary of key advances

The goal of this benchmark has been met for infantile spasms. Since 2007, several new rodent models of infantile spasms have been developed, including acute and chronic models. The acute models of infantile spasms manifest epileptic spasms only during the immediate post-induction period, as a result of either (a) systemic NMDA injection in naïve rats or rats with prenatal exposure to betamethasone or stress or (b) γ-butyrolactone administration (prodrug of a $GABA_B$ receptor agonist) in a Down's syndrome mouse model. Findings from these models suggest that prenatal steroids and stress may render NMDA spasms more sensitive to ACTH (adrenocorticotropic hormone) and that in Down's syndrome, $GABA_B$ receptor signaling may be important for the pathogenesis of spasms. Chronic models of infantile spasms recapitulate several aspects of the infantile spasms syndrome, including chronic spontaneous occurrence of spasms, other seizure types, cognitive and neurodevelopmental deficits. Chronic models include the tetrodotoxin model in rats, the ARX (aristaless related X-linked homeobox gene) knock-in and conditional knock-out mouse models, and the multiple-hit rat model of infantile spasms due to structural lesion. These models support the concept of interneuronopathy in the pathogenesis of infantile spasms (ARX models), the role of mTOR inhibition as a pathogenic signaling pathway and candidate therapeutic target in infantile spasms (multiple-hit model), and the role of developmental desynchronization due to chronic focal activity blockade in the pathogenesis of hypsarrhythmia (TTX model). In preclinical studies using the multiple hit model, carisbamate, the mTOR inhibitor rapamycin, and a new analog of vigabatrin all showed promise for further investigation as potential treatments for infantile spasms.

A model of early life epileptic encephalopathy induced by prolonged exposure to subconvulsant doses of flurothyl and isoflurane has also been published. This model manifests increased epileptic spikes but no seizures during the inhalant exposure and subsequent development of memory deficits.

Factors promoting or hindering progress

- Funding sources contributing to the above progress include: NIH/NINDS, NIH/NICHD, People Against Childhood Epilepsy, International Rett Syndrome Foundation, Heffer Family Foundation, Autism Speaks, Vivian L. Smith Foundation, Questcor Pharmaceuticals, Johnson & Johnson Pharmaceutical Research & Development, Peter Kellaway Research Fund (Baylor Dept of Neurology), MRRDC, American Epilepsy Society / Milken Family Foundation, Children's Hospital of Philadelphia Forderer Foundation Grant, Bloorview Children's Hospital Foundation, Canadian Institutes of Health Research, Hospital for Sick Children Foundation, CURE, March of Dimes.
- Numerous workshops and meetings have helped promote progress and collaborations in this topic. These were included in the programs of the annual meetings of the American Epilepsy Society (2008, 2009, 2010), the 9th European Congress on Epileptology (Rhodes, Greece), 29th International Epilepsy Congress (Rome, Italy), American Academy of Neurology annual meeting (2011).

New or ongoing challenges and opportunities for research

Despite the existence of several rodent models of infantile spasms, at present it is difficult to rely on validation of results across models, given the age, species, and phenotypic differences of the models. Furthermore, the etiologies of infantile spasms are numerous and may impact the phenotypic expression of the syndrome and possibly its response to treatments. Therefore, there is still a need to develop new animal models for infantile spasms of other known etiologies, as well as models with same age, species, and phenotypic characteristics so as to allow across-model comparisons of data. These will be essential both for validating the proposed pathogenic mechanisms of action of the currently available therapies, i.e. ACTH, as well as to identify novel treatments with better efficacy and safety profile on infantile spasms,

emerging seizures, and associated comorbidities. In addition, there is a need for models of other types of epileptic encephalopathies including Lennox-Gastaut syndrome, electrical status epilepticus in sleep, Landau-Kleffner syndrome, Rasmussen's syndrome.

The major challenge however is to optimize the use of animal models of early life epileptic encephalopathies so as to increase their predictive value of identifying new therapeutics for the human clinical syndromes. Ongoing efforts spearheaded by the ILAE, NINDS, and AES aim to address these issues and optimize and accelerate preclinical therapy discovery and successful translation to clinically relevant therapies for seizures, epilepsy, and comorbidities. These issues are being addressed through workshops and task forces organized by NINDS, ILAE, AES and also sponsored by CURE, Autism Speaks, Epilepsy Therapy Project. The major trend-shifting research direction on this benchmark, in the immediate future, will be to *develop and optimize the preclinical use of clinically relevant models of epileptic encephalopathies of infancy and childhood*, so as to increase their predictive value for new therapies for these disorders.

E. Develop new animal models to study epileptogenesis.

3. Develop at least one new animal model that recapitulates the unique aspects of epileptogenesis in the aging brain.

H. Steve White, Ph.D.
University of Utah

Summary of key advances

Epidemiological studies clearly demonstrate that the elderly population is at substantially high risk for the development of epilepsy. When one considers the increasing number of elderly worldwide, the need for a greater understanding of the epileptogenic process in the aging brain is certainly apparent and rising.

As with most of the epilepsies, the marked heterogeneity that exists in the aging population makes it highly unlikely that any one animal model will serve as a broad surrogate for the elderly, thus the need for multiple, etiologically specific models that consider a given population of interest; i.e., the elderly. In addition to stroke (hemorrhagic and ischemic), epilepsy in the elderly is often associated with brain tumors, traumatic brain injury, and Alzheimer's disease.

Importantly, attempts to develop etiologically relevant models over the last decade have been quite successful, and there are now several models that display spontaneous seizures, or at least increased hyperexcitability. For example, models of hypoxia-ischemia, middle cerebral artery occlusion, traumatic brain injury, Alzheimer's disease, and post-implantation of tumor cells are all associated with clinical and electrographic seizures. Each of these models will likely advance our understanding of the pathophysiology of the attendant insult; however, little progress has been made in evaluating the impact that any one of these insults will have when applied to the aged animal. This becomes important when one considers that the pathology associated with a brain insult(e.g., MCAO, TBI, or tumor) could be different depending on the age of the patient, or in this case the animal, at the time of the initial insult. For example, will the incidence and severity of epilepsy that develops following an insult be similar between young and older animals? With that said, the framework for asking this and other questions is now a possibility given that these insults have been shown to produce seizures or epilepsy in younger animal populations.

Factors promoting or hindering progress

Knowledge of the underlying pathology of epilepsy in the aged brain has certainly contributed to the expansion of model development and characterization using etiologically specific insults. Unfortunately, the incidence of post-insult epilepsy in the rodent is, like that of the human, relatively low and variable. Even though the incidence of epilepsy in a model may mimic that of the human, this makes studying epileptogenesis difficult as large populations of animals are required for a thorough characterization of the model.

The limited availability of video-EEG monitoring, along with appropriate resources required for creating, characterizing, and maintaining a population of epileptic animals, has been a real barrier for rapid assimilation of any given model into the wider research community. This has clearly limited the ability to utilize any of the available models in a wider sense.

New or ongoing challenges and opportunities for research

The development, characterization, and utilization of etiologically relevant animal models of aging will have important implications for furthering our understanding of the pathophysiology of epilepsy in the aging patient population. That said, it is important to note that the available models have been developed around a specific etiology associated with aging using mature, but not necessarily aged, animals, and additional research is needed to evaluate the impact that a given insult will have when applied to the aged animal.

With the description of every new model of epilepsy comes an opportunity to utilize the model in the therapy discovery process. Unfortunately, none of the currently available etiological models are routinely employed in this process. Although challenging and expensive, a discussion around this opportunity seems appropriate because it seems unlikely that many laboratories will have the necessary resources or the expertise to develop and fully characterize the potential of a chronic epilepsy model.

F. Test the efficacy of prevention strategies.

1. Test the efficacy of prevention strategies identified above in animal models and in human clinical trials.

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Summary of key advances

- The efficacy of mTOR inhibitors has been tested in various animal models under varying conditions, with mixed results, suggesting their antiepileptogenic effect is dependent on timing and duration of treatment. In humans a single open-label study of oral everolimus did show reduction in subependymal giant-cell astrocytoma volume and seizure frequency.
- The efficacy of adenosine augmentation therapy has been tested in transgenic mice: engineered mice with reduced adenosine kinase (ADK) expression were resistant to the development of chronic seizures after an initial precipitating injury, and focal inhibition of ADK reduced the rate of spontaneous recurrent seizures in transgenic mice in which ADK is overexpressed.
- Prevention strategies using traditional antiepileptic drugs have been tested in both animal models and human clinical trials. In particular, levetiracetam has shown promise in genetic animal models as well as early human clinical trials for prevention of post-traumatic epilepsy.

New or ongoing challenges and opportunities for research

- Testing a prevention strategy is complicated by the diversity of epileptogenic mechanisms, and our inability to differentiate between mechanistic pathways in any given individual or group of individuals. The development of a set of valid biomarkers to measure and signal the stage of epileptogenesis would greatly advance the field.
- Acquired epileptogenesis is likely regulated by multiple molecular pathways, so prevention will require targeting multiple pathways simultaneously.
- The long duration required for a prevention trial is another barrier. Participants in prevention trials would need to be followed for many years, 10-20 years perhaps, in order to determine if epilepsy were prevented, as there is often a long latent period after an acute injury before the onset of epilepsy.
- Any attempts to test an epilepsy prevention strategy following an acute injury needs to also assess functional recovery to insure that the prevention strategy is not impairing recovery.
- For clinical trials the extent of the therapeutic window is a critical issue as it will inform the timing and duration of treatment. Another important issue is the specificity of the window depending on the disease model and treatment.

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

Perspectives on Progress from Area II Chair

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Summary: This Benchmarks area has been quite successful. There have been key advances in diagnostics, therapeutics, and new technologies that are either approved or in various stages of the FDA (U.S.) or CE (European Union) approval processes. The time required to get these new therapies to patients since the first benchmarks meeting is consistent with the expected cycle from invention through pivotal clinical trials and approval. This area is on a trajectory that is steadily producing innovations that are being translated to patients.

Key Advances:

1. *New Medications*: 3 new syndrome specific drugs approved and others on the horizon: Rufinamide (Lennox-Gastaut), Steripentol (Dravet's), ACTH (infantile spasms) approved; Rapamycin for Tuberous Sclerosis.
2. *New Devices*: Anterior thalamic stimulation for refractory partial epilepsy (approved in Europe, 2nd trial requested by the FDA in the U.S.). NeuroPace RNS system, responsive brain stimulation for partial epilepsy completed clinical trials and awaiting FDA panel hearing in early 2013.
3. *New Techologies for Medication Screening*: Most promising: zebrafish provide a rapid, inexpensive transgenic model for high throughput, syndrome-specific screening to yield small molecules that can modulate specific pathways. There is tremendous potential in this area.
4. *New pathways/ pharmacologic targets*: mTOR, JAK/STAT pathway, inflammatory pathways. Ezogabine, neuropeptides, and small molecules.
5. *Diagnostic technologies for mapping epileptic networks and tracking seizure generation and epileptogenesis*: High frequency oscillations (HFOs), microseizures, silicon-based microelectrode arrays, penetrating electrodes, active-flexible multiplexed and dissolvable electrode arrays, connectivity analysis, techniques for studying localized gene expression in specific regions and cortical layers, DTI imaging, morphometric imaging, and source imaging.
6. *New methods to analyze epileptic networks and track biomarkers*: Machine learning, automated analysis methods that eliminate human marking and subjective measurements, cloud computing and data, algorithm and results sharing (**www.ieeg.org**), objective methods to detect and track electrophysiological or imaging biomarkers

Factors Promoting and Limiting Progress:

1. *Factors promoting progress*: Progress in materials science, electrode fabrication, optogenetics, cloud computing, innovative data analysis (machine learning). Shared tissue, gene and data resources are great accelerators of progress. Centers without walls, P01s, Center Grants, training grants, the NeuroNext network concept for facilitating clinical trials.
2. *Factors Limiting Progress*: Lack of data, methods and results sharing; lack of standardization in clinical techniques, or a unifying body to drive standardization. IP protections and policies that limit access to knockouts, specific disease models, and techniques that could hasten therapy development. Lack of incentives for sharing and collaboration that pushes a field forward, perhaps at the expense of an individual investigator's individual benefit (e.g., facilitating research that will not result in first or last authorship for the facilitator).

Challenges: Incentives for groups of investigators to work together to propel a field forward. We need new therapeutic targets and ways to assess them. A limited pipeline of new drugs, and limited ability to test new drugs on refractory patients. The absence of reliable biomarkers for epileptic networks and epileptogenesis. Finding animal models known to have predictive value in human epilepsy. Maintaining expertise and training to conduct excellent clinical trials, including in developing countries where incentives for reliable results may not be in place..

Conclusion: There is rapid and accelerating progress in this area likely stimulated by the Epilepsy Benchmarks process. A major factor limiting progress, other than technical challenges, is a need for fundamental change in the incentives that drive investigator behavior. Optimizing research yield per unit time and dollar invested will likely require fundamental, creative change in government/regulatory agency policy to encourage collaboration, data, algorithm, results and technique sharing.

Area II Benchmarks Progress Summaries

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

1. Define underlying mechanisms of initiation, propagation and cessation of seizures in the epileptic brain as targets for treatment (electrical, biochemical, cellular, molecular, physiological).

Karen S. Wilcox, Ph.D.
University of Utah

Summary of key advances

Considerable progress has been made since 2007 in developing innovative technologies to aid in our understanding of the fundamental questions of: 1) why do seizures start (ictogenesis), 2) how do seizures spread (propagation), and 3) why do seizures stop (cessation). Notable among these developments has been the progress made in electrode fabrication and high resolution recording techniques for human EEGs. These have provided the research community with novel observations, such as micro-seizures and synchronization, which in turn lead to insights concerning ictogenesis and propagation. In addition, a variety of imaging technologies which result in high resolution, high content data have been developed which complement observations made with high resolution EEG. Application of computational neuroscience approaches to these problems, coupled with these innovative technologies, has generated testable hypotheses that have moved the field forward. Finally, animal models of epilepsy and the generation of transgenic animals continue to contribute to our understanding of ictogenesis, propagation, and cessation of seizure activity. However, this benchmark will not have met its intended goal until we can translate our understanding of these complex properties of seizures into novel treatments which either prevent, spatially limit, or rapidly terminate seizures.

Factors promoting or hindering progress

Key factors which have contributed to the progress made in this benchmark include improved biomaterials and fabrication technologies that have enabled the manufacturing of novel electrodes and recording devices, improved imaging modalities with high spatial and temporal resolution, improved computational capabilities and storage capacity, and the beginning of novel collaborative efforts, such as the "International Epilepsy Electrophysiology Portal", which allows for the sharing of data and analysis tools for content-rich EEG data. Novel transgenic animals that allow for imaging populations of select cell types and neural circuits have also contributed to our understanding of seizure initiation and spread. Finally, drawing from developments in social network theory and computational neuroscience and continued collaborations with a variety of scientific disciplines has increased our understanding of the generation, propagation, and cessation of seizures.

Progress has been hindered in this benchmark by the complex nature of network behavior coupled with the complex and varied pathophysiological mechanisms resulting in various forms of epilepsy. Data sets derived from electrophysiology and imaging experiments that can now be performed are huge and content-rich, and innovative analysis tools required for an equally rich understanding of the data have lagged somewhat behind. It is anticipated however that the next decade will see tremendous progress in the development of analysis tools to aid in this effort.

New or ongoing challenges and opportunities for research

As discussed above, perhaps the greatest challenge and the greatest opportunity for this benchmark lies in the translation of new information into effective therapeutic approaches for patients with intractable epilepsy. We need to take our findings from the clinic and the laboratory and develop new therapies that can predict when a seizure is likely to occur, prevent the seizure from actually occurring, or short of that, limit the propagation and spread of seizures to confined regions of brain and then hasten termination. This will no doubt require the development of additional technologies and also the sharing of data among large groups of collaborators. Unlike the past, very few laboratories toil in isolation on these problems in today's world. Collaborations between diverse disciplines (e.g., bioengineering, genetics, pharmacology, computer science, and information systems), and the recognition by funding sources that groups of investigators are likely to move the field forward faster than individual laboratories, will have the greatest impact moving forward.

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

2. Define the functional networks in the brain that are responsible for seizure generation in clinical epilepsy using biosensors, imaging and other methods.

William Stacey, M.D., Ph.D.
University of Michigan

Brian Litt, M.D.
University of Pennsylvania

Summary of key advances

Until recently, technology was extremely limited in its ability to characterize the network properties of seizures. Clinical electrophysiology was restricted to macroscopic recordings from large electroencephalogram (EEG) electrodes. While these electrodes form the basis of clinical epilepsy by determining the regional activity involved in seizures, they have only limited ability to acquire the information necessary to achieve this benchmark. During the past 5 years, many researchers have been developing new technologies that are expanding our understanding of epileptic brain networks. These techniques are: improved electrodes that can sample the brain in much richer detail, analysis of high frequency activity, development of new analytical methods, and improved imaging techniques. Some of these advances have already led to significant contributions to our understanding of seizure networks and are ready for clinical trials, while others are very recent, major technological breakthroughs that will guide research in the next several years.

The past 5 years have seen many groups develop methods for recording seizures with higher spatial and temporal resolution. Clinicians can now implant FDA-approved "microelectrodes" that capture much more data than has ever been available. These electrodes are uncovering complex dynamics and phenomena during seizures. One of the primary focuses of this research is analysis of High Frequency Oscillations (HFOs), a phenomenon that was first recognized in animal models and appears to have a strong relationship to epilepsy. Studies underway are already showing that this information may improve clinical decision-making and epilepsy surgery. The improved resolution also results in enormous amounts of data, which creates a daunting task for analysis. Therefore, another important breakthrough is the continuing effort to develop automated algorithms for data processing. These methods utilize statistical and machine learning tools that have been in use in other scientific areas for many years, for applications like speech recognition. They are capable of analyzing much more data than a human reviewer can perform, and in addition can monitor complex relationships between different brain areas that may help our understanding of seizure genesis. A third and complementary branch of research is the ongoing advancement in imaging. Techniques in functional MRI, diffusion tensor imaging, morphometric analysis, electrical source imaging, and combined EEG-MRI are continually improving, and provide both structural and functional data. New techniques, such as functional MRI linked with optogenetics are poised for a host of new discoveries.

New or ongoing challenges and opportunities for research

While some of these technologies are currently in clinical use, such as microelectrodes and functional MRI, many of them are still in development and require further testing before they can be implemented. By their very nature, they are acquiring new forms of data that still must be validated in the clinical realm. Thus, the continued development of new recording, analytic, and imaging techniques is essential to explore the complex relationships that generate seizures. Although translational to patient care is in some cases a slow process, these breakthroughs literally define the cutting edge of epilepsy research, and are elucidating new understanding about epileptic networks which should lead to new treatment strategies.

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

1. Develop and validate biomarkers and surrogate markers to localize the epileptogenic networks and aid in the discovery and testing of new antiepileptic therapies.

Kathryn Davis, M.D.
University of Pennsylvania

Brian Litt, M.D.
University of Pennsylvania

Summary of key advances

This goal has been partially met and there is exciting progress. There is strong evidence that high frequency oscillations (HFOs) measured in the neocortex and temporal lobe may be biomarkers of epileptic networks and aid in evaluation of epilepsy surgery. These studies, however, are all retrospective; but they associate removal of zones generating interictal HFOs with improved surgical outcome. More careful statistical sampling of these events and prospective studies controlling for resection size are needed to be sure these findings are sound. Other promising advances include functional imaging of brain connectivity, which may reveal abnormalities in epileptic networks. Over the past two years a great deal of excitement has been generated by work associating local neuronal inflammation with epileptic networks and also local expression of specific genes in isolated cortical regions linked to seizure generation.

Factors promoting or hindering progress

Major factors limiting progress in the area of electrophysiology are the lack of a requirement to share data, algorithms and raw signal detection results to allow validation of work across groups. The lack of standardization and agreement on nomenclature for electrode locations, imaging, surgical approaches and results also hinders progress and comparison of methods. In tissue studies there is some increase in the use of shared tissue banks, to allow validation of results, but this is not uniform. Finally, variability in the use of quantitative tools and broad statistical sampling can hamper some studies that require human interpretation of results. The central theme required for progress in biomarkers research is sharing resources and tools, such as methods, data, algorithms, tissue, outcome measures and raw results.

New or ongoing challenges and opportunities for research

New challenges will be finding ways to encourage investigators to pool resources in large, meticulous and sometimes prospective studies to propose and validate biomarkers across centers. There is tremendous opportunity to share some of these resources in information using cloud computing and NIH-funded and other research resources, such as international databases, brain banks, and repositories for algorithms for signal and imaging analysis. There is still a great need for quantitative tools to search for and assess biomarkers in large data sets (including tissue and imaging data) that remove the bias introduced by human interpretation. Large collaborative opportunities, such as NIH-funded “Centers without Walls,” are one example of a creative approach to accelerating biomarkers research.

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

2. Identify new molecular targets for pharmacotherapy development.

Karen Wilcox, Ph.D.
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Summary of key advances

Several new antiseizure drugs (ASDs) have been approved for use over the last decade and some of those, e.g. ezogabine, have very distinct and novel mechanisms of action. In addition, a number of clinical trials are currently in progress to evaluate the safety and efficacy of ASDs that have a diverse array of mechanisms of action. Furthermore, ongoing basic research efforts continue to identify proteins (e.g. neuropeptide receptors) and signaling pathways that may be intimately involved in epilepsy, (e.g., the mTOR pathway, the JAK/STAT pathway, and inflammatory signaling pathways). Thus to some extent, the benchmark has been met, as a number of new potential molecular targets for pharmacotherapy development have been identified. However, it is also becoming increasingly clear that, as a consequence of the heterogeneous nature of mechanisms underlying epilepsy in different individuals, the identification of a single 'silver bullet' therapy for the treatment of epilepsy will be impossible to achieve. Instead, pharmacotherapies designed for specific epilepsy syndromes will most likely be the key to fully achieving this benchmark.

Factors promoting or hindering progress

Foremost among the factors contributing to the progress of this benchmark are the great strides made in the genetics of epilepsy, which continues to identify myriad proteins involved in pathophysiology. These studies point to therapeutic approaches and molecular targets which are not always obvious. In addition, research into inflammatory disorders and various cancers have resulted in the development of 'drugable' small molecules that interfere with signaling pathways now known to also play a role in epilepsy. As such, these molecular entities may be efficacious for either anti-epileptogenesis or disease modification of existing seizure disorders, and therefore represent significant progress in our understanding of epilepsy.

Hindering our progress in pharmacotherapy development is the lack of sufficient animal models that are *known* to have predictive value in humans with respect to the efficacy of novel compounds. While the maximal electroshock model of seizures was validated by the clinical efficacy of phenytoin shortly after its discovery, animal models of spontaneous seizures currently used for therapy discovery have not necessarily been validated for predictive value. Efforts to pharmacologically vet existing and new models of epilepsy would be useful to determine if preclinical studies will result in the development of ASDs with novel mechanisms.

New or ongoing challenges and opportunities for research

While a number of new anticonvulsants have come to the market in the last decade, it is still estimated that between 25-35% of patients with epilepsy do not have adequate seizure control. Furthermore, the side effects of taking these compounds are often intolerable to the patients who must take these drugs to control their seizures. Therefore, there is an ongoing need to identify new therapeutic targets and new pharmacological entities for those targets. The continued emphasis on basic research to develop novel technologies and to identify mechanisms underlying the epilepsies will no doubt continue to reveal new insight into approaches for the symptomatic treatment of epilepsy. A unique opportunity also exists with respect to the development of transgenic animals that uniquely model specific forms of epilepsy or syndromes. These may provide useful new screening tools and could provide unique validation of therapeutic approaches that target specific molecular deficits (e.g., in Dravet syndrome).

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

3. Develop valid screening strategies and biomarkers and surrogate markers (e.g., genetic, pharmacogenomic, electrophysiologic, imaging, biochemical) to identify patients who are likely to respond to, or develop adverse effects from specific therapies.

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Summary of key advances

The goal has not yet been met. During the past 5 years, research has focused on pharmacogenetic rather than metabolomic, imaging, or electrophysiologic markers of drug response. The major pharmacogenetic advance has been validation of the association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome in specific Asian populations (e.g. China, Thailand and Malaysia), but not in European or Japanese patients. With a 92% sensitivity and a 98% negative predictive value, one study suggested that specific screening for HLA-B*1502 may be useful and cost efficient in certain populations. Other studies reported a potential association between HLA-B*1502 and the development of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis for other aromatic anticonvulsants (phenytoin, oxcarbazepine and lamotrigine). A second HLA locus (HLA-A*3101) was found to be associated with a variety of carbamazepine-induced hypersensitivity reactions. The risk of these reactions increased from 5.0% to 26.0% when patients had the HLA-A*3101 allele and decreased to 3.8% when the allele was absent.

In contrast, no clear genetic, electrophysiological, or imaging markers of drug response have been found. Since 2007, multiple studies and meta-analyses have examined whether specific polymorphisms in the ABCB1 gene are associated with drug response. Despite initial enthusiasm, 15 subsequent studies on ABCB1 polymorphisms in different ethnic populations, with different AEDs and epilepsy types, as well as different definitions of drug resistance have been unable to clearly confirm the association. A 2008 meta-analysis of 11 case control studies involving 1646 patients with drug resistant epilepsy and 1725 controls found no significant association between ABCB1 polymorphisms and AED resistance. More recent studies did not find a direct association between ABCB1 polymorphisms and AED resistance. Some studies have examined how polymorphisms in various sodium channel genes correlate with drug response. In 471 Chinese epilepsy patients (272 drug responsive and 199 drug resistant) there was an association between SCN2A IVS7-32A>G (rs2304016) A alleles and drug resistance. One study failed to find an association between pre-treatment metabolomic profiles and response to therapy.

Factors promoting or hindering progress

The rapid technological advancements coupled with the dropping costs of genetic sequencing as well as improved data processing of complex dynamical systems properties have energized investigators worldwide to continue the search for AED pharmacogenetic biomarkers. Most likely few allelic variants in any one gene or test will have a large enough impact to alter a phenotype in an easily recognizable fashion. The development of global pathway approaches that simultaneously consider polymorphic variations in all relevant genes, proteins, and metabolites, as well as linkage to phenotypical, electrophysiological and imaging changes, have provided researchers with a new approach to interpreting and thinking about these new complicated data sets. The optimal study design and subsequent statistical methods needed to use this systems approach is not yet fully delineated, but represents an exciting frontier in biomarker research.

The current lack of any accepted biomarkers for antiepileptic efficacy, tolerability or safety (other than HLA*1502) is most likely related to methodological challenges. Ideally, pharmacogenetic association studies in epilepsy would occur in a large genetically and phenotypically homogenous population who were followed prospectively from onset, treated with the same medication in the same fashion, assessed using standardized objective methods for seizure freedom determination, and classified by pre-defined definitions for treatment resistance. These pharmacogenetic assessments

would be primary or secondary outcomes rather than being exploratory and include examination of dynamical changes in electrophysiological and imaging data. While there has been no progress in how to read EEGs or MRIs over the last decades, the progress in genetic and genomic research, machine learning, and complex system's characterization has also provided additional tools that may permit characterization of additional complex system shifts in EEG, regardless of seizures or spikes. There are no current published pharmacogenetic studies meeting all these criteria. Without these types of studies, identification of more AED biomarkers will remain serendipitous. The 2010 ILAE report of a standard definition for drug resistant epilepsy is a first step to standardizing outcomes.

New or ongoing challenges and opportunities for research

Clinically focused classification frameworks need to be developed to detail acceptable criteria for an AED biomarker. Once these classification frameworks are established, the chance of identifying and confirming valid screening strategies, biomarkers and surrogate markers for AED response over the next 5-10 years depends directly on the development of large multicenter collaborative research teams. These teams will prospectively implement standardized treatment strategies in homogenous new-onset epilepsy populations, evaluate outcomes using pre-determined objective measures, and implement the latest genomic, proteomic, metabolomics, electrophysiological, and imaging techniques on samples obtained prior to and during therapy. Larger datasets may also predict overall state changes in patients who are more susceptible to epilepsy, and these state changes may be measured without visible changes on phenotypic data, including EEG or functional imaging. These types of studies should include pharmacoeconomic evidence of potential future cost savings.

Given the challenges and costs of developing new medical therapies for epilepsy coupled with the costs of drug toxicity and delayed efficacy, it makes sense to focus more attention on the identification and validation of AED response biomarkers. Additional studies are needed to examine the cost-effectiveness of pharmacogenetic testing, develop novel tools to combine clinical and genetic data, and address the educational needs of clinicians who must implement these test results into actual practice. These types of studies may provide additional advanced screening and monitoring technologies for treatment response in clinical practice.

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

1. Determine factors and approaches associated with best outcomes for surgical therapies.

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Summary of key advances

In the past five years, numerous studies have been published addressing, at least in part, the goal of improving surgical outcomes in patients with treatment resistant focal epilepsy. Despite these continuing efforts, the goals of this benchmark have not been reached. Although we believe this is a critical benchmark, substantial barriers to future progress persist.

The literature addressing this benchmark continues to focus, as it historically has, primarily on the combination of new diagnostic tests and new ways of analyzing/interpreting current diagnostic tests. Areas of progress have included magnetoencephalography (MEG) and magnetic source imaging (MSI), functional magnetic resonance imaging (fMRI), quantitative approaches to structural MRI analysis, and high field (e.g. 7 Tesla) MRI imaging. In addition, novel ligands for PET studies exploring beyond glucose metabolism have been utilized in epilepsy (e.g., alpha-methyl-tryptophan for patients with TSC). All of these efforts have been demonstrated to provide additive or complementary diagnostic benefit in patients with epilepsy through different studies. Similarly, increasing focus and effort has been directed toward high frequency oscillations and microelectrode recordings in humans and in models of epilepsy. These important observations and studies garner new insights as well as raise questions about how seizures are generated and spread within the human brain. New approaches to EEG (particularly intracranial EEG) analysis in the future are also suggested by these data and many centers now incorporate review of high frequency oscillations into their surgical decision making process. These important studies are inherently limited by the need to have patients undergoing epilepsy surgery in centers with the technical expertise to safely and confidently obtain these data; as a result, data from a wide range of seizure types and lobar localizations remain relatively limited.

New or ongoing challenges and opportunities for research

Although steady progress can be seen across the past five years, we have identified several key barriers to significant advances in the surgical treatment of epilepsy. The literature and many new treatment modalities (e.g., stereotactic radiosurgery or thermal ablation) continue to focus largely on temporal lobe epilepsy. Numerous groups have suspected that the utilization of anterior temporal lobe resections has declined over the past three decades, and a recently published population-based cohort study from the Mayo Clinic supports this observation. There are many potential reasons for this shift in surgical procedures, but for benchmark purposes, a couple of broader areas should be highlighted. First, most studies have not used intent-to-treat methodology. These studies have focused on a group of patients selected to undergo a particular procedure often after a decision was made that they were surgical candidates. This provides a substantial barrier to understanding the potential reasons underlying a change in temporal lobectomy rates; moreover, it largely neglects the group of patients with non-surgical treatment-resistant epilepsy. Omitting these patients from analyses may lead to flawed conclusions regarding potential characteristics (EEG, imaging and clinical) that would predict favorable surgical outcome. Second, these data highlight the need to identify and characterize the treatment-resistant epilepsies currently seen in centers across the United States. If temporal lobe epilepsy is actually less commonly seen (or just less commonly treated surgically), the seizure type(s) that are more prevalent now (particularly neocortical epilepsies) need to be both identified and prioritized in future surgical studies.

The classification of seizures and epilepsy remains a challenge and the subject of significant debate. A framework for classifying treatment resistant patients across centers in a manner that can be systematized and replicated will facilitate comparison of approaches. Studies continue to have heterogeneous patient populations and variable approaches to the pre-surgical evaluation. As a result, the applicability of any one advance across a wide spectrum of patients with treatment-resistant epilepsy in centers across the United States (and beyond) remains a largely unanswered question. Similarly, the additive benefit when multiple novel approaches are utilized remains largely uninvestigated.

Another significant barrier to the long-term goal of utilizing the advances over the past half-decade in clinical practice is the highly technical nature of some of the analysis techniques proposed and/or the limited availability of the test mechanism itself. Quantitative analysis techniques frequently require substantial off-line processing which, in turn, requires both human and computational resources. MEG, PET, and high field MRI require specialized equipment that is often not available in or near all centers.

Identifying key factors that optimize the selection for and utilization of surgery for treatment resistant epilepsy remains an incomplete benchmark goal. The challenges described above represent, if addressed by the epilepsy community, several key areas which should facilitate even greater advances in the next five years.

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

2. Develop new approaches (e.g., gene therapy, brain stimulation, cellular therapy, pharmacotherapy) for targeted therapies.

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Summary of key advances – brain stimulation

Electrical stimulation of the brain remains a therapeutic approach that attracts great interest in spite of the minimal benefit that has been seen in clinical trials to date. There are three primary types: deep brain stimulation, intracranial cortical stimulation, and peripheral nerve stimulation. To date, deep brain stimulation has involved either the thalamus or the hippocampus, and only thalamic stimulation has been organized into a large-scale trial. Both sites are stimulated at a regular intermittent frequency (typically greater than 100Hz). The few reports of hippocampal stimulation have not shown a major effect. Although there have been some reports of seizure freedom, they have not been replicated in small trials (all are typically 5 patients or fewer). The Medtronics SANTE trial of stimulation in the anterior thalamic nucleus showed significant seizure reduction over the long term, but the goal of seizure freedom was not achieved, and the majority of patients saw little benefit. Thalamic stimulation has been approved in Europe but not yet in the U.S.

Cortical stimulation has taken a different approach by stimulating only at times when the electrodes detect a potential seizure in its early stages. As with the deep brain stimulation studies, slight benefits have been reported from this approach, but it is unclear whether this closed loop, reactive stimulation will be approved for clinical use.

Vagal nerve stimulation has been available for many years, and more recently there has been a report of trigeminal nerve stimulation. This alternative method reports similar efficacy to vagal nerve stimulation with responder rates around 50% (a responder is defined as having greater than 50% reduction in seizure frequency). Seizure freedom, although reported, remains rare for both methods.

There are some animal studies using acute stimulation in various regions (hippocampus, corpus callosum, thalamus) that report a positive effect on induced seizures, but it is unclear how those may translate to the clinical setting. There are no reports of major successful studies in animal models with epilepsy.

New or ongoing challenges and opportunities for research – brain stimulation

There remains a general belief that brain stimulation will ultimately prove successful, but the data have not yet provided much hope. Epilepsy has multiple causes and many different neuronal circuits, so it is unlikely that one stimulation approach will be successful for all. We don't know where or how we should stimulate for any of the syndromes. Until there is a better understanding of how stimulation affects the brain to alter seizures, and what stimulation protocols are needed to reduce seizure activity, brain stimulation trials will largely be based on unverified presumptions about how stimulation might alter circuit physiology. It may be ultimately more effective to focus on realistic animal models of different forms of epilepsy to define potential targets and physiological markers for effective stimulation. With this information, it may be easier to design protocols that will deliver the needed physiological changes in the key circuits.

Summary of key advances – gene therapy

Gene therapy remains the subject of many studies, and the repertoire of approaches continues to expand. The basic concept is to alter the physiology of key neuronal populations so that they are less likely to support seizure activity. The original approach was to implant cells that had been transfected with a particular gene, with the goal to overexpress a particular protein. There have been many attempts to transfect cells, typically with a tagged adenovirus so that the basic physiology of the neuron is altered. The proteins most commonly targeted for transfection have included $GABA_A$, NPY, and galanin, but there is now also interest in voltage gated ion channels and their modulators. The majority of these studies demonstrated the ability to introduce a new protein into the cell, and there was typically associated alteration in the physiology of the neuron or, when using an epilepsy model, an appropriate reduction in seizure measures (frequency, duration, behavioral severity). More recently, antisense RNA has been used to reduce protein expression.

New or ongoing challenges and opportunities for research – gene therapy

All of these observations have created excitement about the potential for this approach, but there have been a number

of observations that suggest clinical application of this approach is in the distant future. One of the more common observations is the transient nature of the effect: there is a clear effect on the measure early after transfection, but over time (measured in weeks) the changes gradually subside, suggesting that this particular approach to epilepsy therapy may have limitations when applied to chronic disease. Another observation is that there is little control over which cell population will express the transfected gene, or how altering that particular neuronal population will affect overall circuit function. Further inhibiting a population of inhibitory interneurons may have an opposite effect to that desired. Another concern raised is the lack of proper controls, in that in some cases it is not clear whether the effect derives from the transfected protein or whether it is secondary to the transfection itself or to a systemic response to the transfection. In terms of the antisense RNA approach, although conceptually very attractive and often successful in *in vitro* systems, it has been far more difficult to demonstrate consistent effects *in vivo*.

The potential to change circuit excitability through the manipulation of gene expression or the introduction of new genes remains a very attractive approach to treating and, potentially, curing epilepsy. However, there are many obstacles to achieving these goals in a mature nervous system: transient nature of protein expression, compensatory changes in other neuronal populations that may negate the effects of transfection, altering the physiology of groups of neurons that result in a net increased propensity to support seizures. Further development of this line of therapy may require breakthroughs in technology that can target specific neuronal populations in selected regions and create more lasting, or permanent, changes. More information about how these interventions affect the seizure circuits at the micro and macro level and for how long may be the best initial steps for developing genetic interventions for epilepsy.

Summary of key advances – focally targeted therapies

Focally targeted therapies that deliver molecules on an ongoing basis to a key point in the seizure circuit have had some interest in recent years. The concept behind this approach is that one can avoid many side effects by delivering drugs to one area of the brain. Some compounds with a defined mechanism of action could be quite effective at suppressing seizure activity, but systemic effects or effects in “normal” brain regions limit their clinical utility. Another reason for focal delivery is that some promising approaches do not cross the blood brain barrier. There are two main components to focally targeted approaches: the choice of pharmacologic targets and the mechanisms of drug delivery. There are also two challenges: drug distribution within the target region and replenishing the drug reservoir from external sources. Almost all of the work in this area has been in animals.

New or ongoing challenges and opportunities for research – focally targeted therapies

Drug distribution is a significant issue as the drug is delivered from a point source to a volume that is relatively large, so that the fall-off in concentration from the delivery site is considerable. Convection enhanced diffusion, essentially pumping the drug-containing solution at higher rates, has the potential to increase the amount of drug delivered and improve the concentration gradient. However, it currently remains a hypothetical approach to focal drug delivery, as it is not clear whether it can deliver adequate concentrations to the target region. Another method has been local transdural or subdural drug delivery, and devices have been successful in suppressing experimental acute seizures in which the site of seizure induction was known. How such an approach would work for a larger and less well-defined seizure focus is unclear. Another reported approach for focal drug delivery uses local sources of ultraviolet light to uncage compounds that are delivered systemically. Although the approach has been successful *in vitro*, questions have been raised about the long-term safety of intermittent ultraviolet light exposure in the brain. However, the concept of converting a systemic pro-drug to an active drug through a focal physical stimulus is intriguing. This approach would require a close collaboration between medicinal chemists and device makers.

Replenishing the drug supply is also a key issue. One strategy has used rods embedded with drug or with cells that produce an antiepileptic molecule (e.g., adenosine). These approaches were limited by the relatively rapid loss of drug or death of adenosine-producing cells. Chronic infusion therapy through an implanted catheter has been used for baclofen, pain relievers, and insulin. They are delivered through an external pump with a drug reservoir that is regularly renewed. For this method, a target region and a drug need to be identified and tested before a clinical trial can be considered. The likely volume of tissue that would require therapeutic concentrations of drug to suppress spontaneous seizures is much greater than the volume immediately surrounding the catheter tip, so it is unclear how effective concentrations can be achieved. The issue of potential infection from a tube that connects the outside world to the central nervous system is also of concern, so focal delivery must address this issue as well.

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

3. Develop higher-throughput cost-effective models for screening pharmacotherapies for specific types of epilepsy.

H. Steve White, Ph.D.
University of Utah

Summary of key advances

The approach utilized over the last eight decades for identifying new therapies for the symptomatic treatment of epilepsy using established animal seizure and epilepsy models has clearly been successful, and a number of new chemical entities are now available for the treatment of partial seizures. Further, three drugs have received approval for specific seizure types: Lennox-Gastaut Syndrome (rufinamide) and infantile spasms (stiripentol and ACTH). Nonetheless, selecting the most promising candidate drug using animal models is an iterative process that is resource intensive and can take months to years. There is also no guarantee that an identified candidate will be effective in a specific patient population until the appropriate clinical trial is conducted. Thus access to etiologically appropriate, high through-put systems for screening novel therapies has the potential to shorten the discovery process.

In a few short years, the zebrafish (*Danio rerio*) model has emerged as an exciting and potentially viable model for moderate- to high-throughput screening for compounds that might have anticonvulsant activity. Several features of the zebrafish model make it highly attractive for early screening. Notably, the costs associated with maintaining a zebrafish colony are small relative to a rodent colony; seizure-like activity can be evoked in larval and adult zebrafish by various pharmacological and genetic manipulations; and the zebrafish model is an excellent platform to produce large numbers of fish with known mutations found to be associated with human epilepsy and other disease states. Herein lies an important opportunity for creating a high-throughput seizure/epilepsy-type specific *in vivo* model system for large-scale screening.

Factors promoting or hindering progress

The zebrafish system offers substantial advantages over the rodent in the way of cost and access to genetic manipulation. However, in contrast to rodent models, the seizure phenotype of the zebrafish has not been correlated to the human epilepsies and the pharmacology is incomplete. In the zebrafish model, drugs are introduced into the bath (i.e., the water in which the fish swim), and there is no guarantee that a drug is always bioavailable through this application. That said, many of the practical barriers of drug administration and evaluation are being minimized, and methods are available for assessing seizure-like behavior using sophisticated tracking systems. The zebrafish offer a distinct advantage in that they have the potential to become relatively high-throughput screens that can facilitate lead optimization at a much reduced cost; thus reducing the financial burden, which continues to be an important consideration in drug discovery.

New or ongoing challenges and opportunities for research

The availability of a high-throughput etiologically appropriate *in vivo* model system that incorporates knowledge of the disease state into its platform would be an important asset to the drug discovery process. The ability to quickly identify the most promising compounds with biological activity represents an important step in conserving valuable resources. Further, the ability to generate a large population of genetic mutants for selective target-based screening represents a substantial future opportunity for drug screening utilizing a seizure type or epilepsy syndrome-specific model. To date, this approach is not widely utilized nor validated. Moving from novel “hits” identified in a much reduced system (like the zebrafish model) to translating their activity to the rodent and subsequently to the human is the most important aspect of any screening approach; unfortunately, it is also the most challenging. The extent to which the zebrafish model, with all of its obvious advantages, can be utilized to identify therapies (genetic or pharmacologic) that might lead to a cure or disease-modifying therapy is not known but represents an effort certainly worthy of consideration.

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

4. Initiate clinical trials of new, modified, and combination approaches to enhance cure rates.

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Summary of key advances

This goal has only been partially met. Over the last five years some advancement has occurred in the development of new chemical entities and other therapies for treatment resistant epilepsy. However, this advancement has been limited. Of the drugs that were entered into clinical development from 2007-2012, only one has been approved for use in the US (retigabine) and one in Europe (eslicarbazepine). Several (brivaracetam, perampanel, YKP3089, VX-765) continue in development. Several compounds (seletracetam, carisbamate, JZP-4, ICA-105665, ganaxalone, BGG492) are not currently progressing in development. Neither of the new devices in development (responsive neurostimulator [RNS] and thalamic deep brain stimulator [DBS]) has been approved. Notably, of novel chemical entities, only YKP3089, and VX-765 entered and stayed in development during this 5 year period.

New or ongoing challenges and opportunities for research

The pipeline of new drugs that will ultimately proceed into development seems to have slowed down, and there is an urgent need for novel chemical entities and novel devices that will provide a greater likelihood of complete control of seizures in patients who are currently treatment resistant. Challenges also continue related to the reduced ability to recruit patients into clinical trials (partly due to the availability of 17 drugs for the treatment of epilepsy), increasing demands for large numbers of centers to perform trials, and globalization of the clinical trial enterprise. This produces increased heterogeneity across patients in a trial, which ultimately may threaten the integrity of the trial. Data now support a decrease in investigator expertise and oversight in some pivotal epilepsy trials performed in the private sector. The absence of biomarkers or early indicators of success makes it difficult to design efficient proof-of-concept studies that would allow selection of the best drugs to proceed into clinical development. This, in turn, increases the cost of development and reduces incentives to develop novel epilepsy therapies.

Several pipeline conferences were held to discuss clinical trial methodology and pipeline development. An NINDS workshop was held to identify roadblocks to advances in clinical trials and to new drug development. Several initiatives are ongoing as a result of this workshop, including efforts to develop novel clinical trial methodology, and attempts to allow approval of drugs for monotherapy through a simplified regulatory pathway. In addition, efforts are underway to pool data from placebo arms of randomized pivotal trials of new chemical entities, which may identify causes for rising placebo effects. The ILAE has an active ongoing task force addressing regulatory roadblocks.

The recent creation of NeuroNEXT, an NINDS supported network of investigators and infrastructure designed to increase the efficiency of clinical trials, is expected to facilitate patient recruitment and retention, to increase the quality of neuroscience clinical trials, and to enable public-private partnerships. It is not yet clear whether they will undertake any epilepsy trials. Provision of adequate training for new sites and new investigators is also needed.

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

Perspectives on Progress from Area III Chairs

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Over the past 5 years, there has been ample demonstration, in multiple settings and using a variety of approaches, of the high burden of many different conditions and disorders in people with epilepsy (PWE) relative to people without epilepsy. The bidirectional nature of these comorbid conditions (sometimes preceding, sometimes coming after the onset of seizures) has led to a realization that these disorders may reflect aspects of the dysfunction involved in the epilepsy itself. These disorders may have a profound impact on the quality of life and success of PWE. The majority of the evidence has focused on cognitive and behavioral comorbidities, but progress has also been made in the understanding other comorbidities, particularly sudden unexpected death in epilepsy (SUDEP), mortality in general, reproductive health and risks, sleep disorders, and other medical disorders.

Epidemiologic studies have demonstrated that psychiatric comorbidities are relatively frequent in PWE, with life-time prevalence rates averaging 35% for a psychiatric disorder. In adults, depression and anxiety disorders are the two most frequent psychiatric comorbidities. Recent randomized trials of treatment of depression in PWE has shown that the standard therapies in the general population of people with depression are effective in people with epilepsy and do not appear to lead to seizure exacerbation. This addresses a major barrier to treatment as concerns over potential seizure exacerbation often led to withholding of treatment in the past.

Information from structural and functional neuroimaging techniques has increased our knowledge of widespread brain networks which are implicated in seizure generation and propagation and which likely contribute to cognitive, behavioral, sleep, and other disorders. Animal models of cognitive and behavioral comorbidities in acquired and genetic epilepsies, in both immature and mature animals, have been developed. These models, and identification of some potential mechanisms underlying the behavioral and cognitive comorbidities they exhibit, should provide new opportunities to test approaches to the treatment of comorbidities. In pediatric patients, intellectual disability (ID) is the single most common comorbidity. While ID is in large part due to the underlying cause of the epilepsy, increasing evidence demonstrates that seizures in the developing brain are themselves responsible for a substantial component of the ID. The implications for prevention are considerable.

There have been important discoveries and research efforts that considerably improved our understanding of potential SUDEP mechanisms and risk factors. There has been unprecedented interdisciplinary collaboration between basic and clinical research resulting in rapid translation of bench science discoveries into clinical investigations, preliminary screening of candidate mechanisms (neuro-cardiac, autonomic, and respiratory compromise) and molecular risk factors (e.g., autonomic function screen and long QT gene screens), and testing of potential preventative interventions (e.g., serotonin re-uptake inhibitors (SSRIs) in patients with epilepsy). Although preventative strategies for SUDEP are undergoing study, none has been validated. The NINDS initiative for SUDEP funding, Partners Against Mortality in Epilepsy (PAME) Conference, and the development of two SUDEP registries have been key factors in furthering knowledge in this area.

Understanding how to treat pregnant women with epilepsy and the impact of antiepileptic drugs on the developing brain *in utero* is integral to the care of women with epilepsy and has received much study in this time period. The NEAD study has demonstrated that the developmental impact of exposure to some drugs *in utero* may persist for years after birth. 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. Emerging data from multiple

hospital- and population-based registries better defined the risk of teratogenic, particularly neurodevelopmental, effects of antiepileptic drugs.

Of the 1% of the US population diagnosed with epilepsy, it is suggested that 5 to 20% actually have Nonepileptic Seizures (NES), and current estimates suggest that 10% of adults and 30% of children with NES also have epilepsy. Considerable progress has been made in understanding the risk factors of and treatment options for NES. Methods and physician training are needed to arrive at quicker recognition of NES and avoid what may often be years of misdirected therapy, including surgical evaluations, for uncontrolled events.

Tremendous progress has been made in the comorbidities of epilepsy, ranging from the recognition of their importance and their potential clinical implications, to a large diverse effort to understand the underlying mechanisms and identify strategies for treatment. Yet, many challenges remain. There is a continued need for hypothesis-driven research on comorbidities to define molecular predictors, biomarkers, diagnostic screening paradigms, and in turn, for translation into clinical practice. More interdisciplinary or cross-disciplinary research teams and collaborations are also needed, including prospective, multicenter studies to supplement existing systematic case registries. To further optimize preclinical models that are validated and resemble the human condition, endpoints (outcomes) that are measurable, reliable, and relevant to the human disease need to be developed. Likewise, better technology is needed to permit *in vivo* monitoring of biomarkers relevant to comorbidity prediction, progression, and treatment response in preclinical studies. New analytical platforms will certainly be important as well in future discoveries of new candidate genes for comorbidities. Finally, programs that foster career development for researchers interested in comorbidities will be needed for uninterrupted progress.

Area III Benchmarks Progress Summaries

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

1. **Determine the types, frequency and severity of various comorbidities in the general population of people with epilepsy.**
2. **Identify at least one new susceptibility factor each for cognitive, neuropsychiatric, and other medical comorbidities in people with epilepsy.**
3. **Delineate the natural history of comorbidities in epilepsy including the nature of the relationship between specific comorbidities and the underlying causes of epilepsy, specific features of epilepsy (e.g., age of onset, frequency of seizures, interictal epileptiform abnormalities), and treatment (e.g., antiepileptic drugs (AEDs), surgery).**

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Summary of key advances

Most of the progress made in this benchmark area has been to demonstrate the increased prevalence of a large variety of conditions in people with epilepsy relative to people without epilepsy. The evidence accumulated has continued to focus on cognitive and behavioral comorbidities but has also considered other medical comorbidities, accidents, and various causes of death (e.g., SUDEP, homicide, suicide, natural causes), as well as health behaviors. There has been a plethora of reports demonstrating that people with epilepsy have greater comorbidity burdens than others. The goal of examining relative prevalence for most behavioral and psychiatric comorbidities has largely been met.

[An exception is understanding the relationship between autism and epilepsy, which has been a politically charged topic. Various authors have pointed out the thorny methodological issues in studying autism, especially with the new proposed definition in the DSM-V. Other serious concerns include: (a) autism is a comorbidity of intellectual disability (ID) which is in turn a comorbidity of epilepsy; (b) autistic features are nonspecific and commonly seen in individuals with ID, and their presence alone does not constitute autism; (c) diagnostic trends and use of the autism diagnosis to obtain special education services has made reliance on a clinical diagnosis for research purposes particularly problematic. There is no evidence to support an independent association between autism and epilepsy in the absence of ID at this time.]

Most of the existing evidence for increased comorbidity burden in epilepsy compares persons with epilepsy to healthy controls; some, but much less, evidence compares epilepsy to general medical illnesses; and very little, if any, evidence compares epilepsy to other neurological disorders to address issues of epilepsy specificity. There remains no population-based investigation of cognition in adults with epilepsy, and patterns of neurobehavioral comorbidities shared across different epilepsies or specific to certain syndromes remain uncertain. More is known in this regard in children with epilepsy. A substantial proportion of the literature on comorbidities in epilepsy is based on analyses of administrative data sets. These are good for demonstrating large population trends but are limited for providing the detail necessary to do more than establish trends. There has been relatively no emphasis on determining the severity of conditions, in part because of the reliance on administrative data. Progress in this area will require different approaches.

Clinical evidence for the deleterious role of seizures themselves in the developing brain has been demonstrated in several surgical series, one pharmacologic trial, and a community-based study. Neurophysiological evidence that seizures affect cortical excitability up to 24 hours before and 24 hours after a seizure has highlighted the importance of the interictal period, which was the subject of a recent American Epilepsy Society symposium. Additional studies have demonstrated the increased prevalence of depression in the context of uncontrolled seizures, but not whether one is the consequence of the other. There have been some studies of brain morphology as correlates of subtle cognitive variations in children with otherwise uncomplicated epilepsy, and functional imaging techniques are beginning to be used as well. For the most part, the findings from these studies have yet to be replicated. In specific disorders known to

cause epilepsy, the underlying disorder itself, independent of seizures, has also been shown to increase the risk of cognitive impairment (e.g., tuberous sclerosis). Finally, at least one study found that a family history of epilepsy (a proxy for a genetic basis of the epilepsy) was a risk factor for behavioral problems in children with epilepsy. Understanding the reasons for the increased levels of comorbidities in people with epilepsy is an area that still requires further work; however, it will require dedicated efforts and not simply adapting existing datasets for the purpose.

Twelve studies from 1990 to the present have demonstrated a bi-directional association between epilepsy and various cognitive and psychiatric comorbidities, including depression, suicidality, psychosis, schizophrenia, general psychiatric disorders and psychiatric hospitalization. This provides greater impetus to pursue the underlying mechanisms given the implication of shared causation between various comorbidities and epilepsy. As a related example, sleep has become an increasingly important area, and may be relevant to understanding certain mechanisms underlying epilepsy, seizure exacerbation, and even sudden death. Alternatively, there may be different mechanisms and possibly different implications for intervention. Dedicated efforts are required at this point including expanding beyond secondary analysis of existing data. Relatedly, reports from both pediatric and adult epilepsy investigative groups have now demonstrated the presence of cognitive, academic, psychiatric and social comorbidities at or near the onset of epilepsy, with several reports demonstrating existence of these comorbidities antecedent to the first recognized seizure. The short (years) and long term (decades) courses of these early-identified comorbidities remain unclear.

New or ongoing challenges and opportunities for research

Progress in this area has likely been impeded by reliance on existing datasets (including administrative) and secondary analysis of data collected for other purposes. Methodological sophistication often cannot compensate for these matters, and there is a need to clearly articulate the appropriate data quality and level of detail required for validity in this area. Targeted investigations to produce such high quality data should also be encouraged. An especially difficult intersection is that between clinical-epidemiological research and studies in animal models. The development, utility and applicability of animal models of comorbidities would be greatly facilitated by a precise characterization of the human condition—an important reason to press on in this area.

B. Identify predictors and underlying mechanisms that contribute to comorbidities.

1. Identify and utilize promising techniques and paradigms from other areas within the behavioral neurosciences (e.g., structural and functional neuroimaging, EEG, magnetoencephalography (MEG), genomics) and apply at least two of these approaches to the study of cognitive and behavioral co-morbidities in epilepsy.

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Summary of key advances

Over the past 5 years, the application of structural and functional neuroimaging techniques have increased our knowledge of the pervasive nature of cognitive and behavioral comorbidities in epilepsy as well as the co-existence of widespread brain network abnormalities. For example, in adults with temporal lobe epilepsy (TLE), the link between the degree of hippocampal atrophy and memory deficit is well documented but new studies have revealed that considerable extratemporal lobe abnormalities are correlated with other cognitive domains (e.g., executive function, language, and psychomotor speed). In children with epilepsy, neuroimaging techniques have delineated cognitive behavioral abnormalities relating to structural and functional deficits within specific epilepsy syndromes (e.g., juvenile myoclonic epilepsy) and in more heterogeneous epilepsy populations. Such findings raise the possibility that comorbidities in pediatric epilepsy have shared and syndrome-specific biological underpinnings. Another area of advancement is the finding of widely distributed functional and anatomical abnormalities associated with mood and psychotic disorders in TLE, including in the amygdala, hippocampus, orbital frontal cortex, cingulate gyrus, subcortical regions and brainstem.

New or ongoing challenges and opportunities for research

- Most of the studies have used a single neuroimaging modality. Future studies combining several techniques will provide a better understanding of the neuroanatomic correlates of cognitive and behavioral problems. Application of genomic techniques in conjunction with neuroimaging may elucidate common pathogenic mechanisms of seizures and comorbidities.
- Cognitive and behavioral abnormalities are present at or prior to the diagnosis of epilepsy, but there is a paucity of studies in children with new-onset disease. To date, of the eight studies examining children with new-onset epilepsy, only two studies analyzed the relationship between structural abnormalities and cognitive performances. More longitudinal studies are needed to clarify whether structure-function relationships identified in cross-sectional studies contribute to long-term adverse outcomes.
- To develop preventative strategies, the natural history of structural and cognitive outcomes from the time of epilepsy diagnosis (and the independent contributions of ongoing seizures and epilepsy treatments) must be better characterized. In essence, neuroanatomic biomarkers are needed to measure progress and outcomes in people with epilepsy.

B. Identify predictors and underlying mechanisms that contribute to comorbidities.

2. Develop and validate at least one animal model of a comorbidity of epilepsy.

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Summary of key advances

The goal of this Benchmark has been met. Since 2007, there have been many publications describing cognitive and emotional comorbidities in animal models of both acquired and genetic epilepsies, in both immature and mature animals. These include depression-like symptoms in the lithium-pilocarpine model of temporal lobe epilepsy (TLE) and in the WAG/Rij genetic model of absence epilepsy. Deficits in learning and memory, autistic-like behaviors, depression and anxiety were identified in the GAER (Genetic Absence Epilepsy Rats from Strasbourg) model of generalized epilepsy, and these behaviors appeared to be independent of seizure onset. Learning deficits and autistic-like behaviors were found in an animal model of symptomatic infantile spasms that were suppressed by high-dose pulse rapamycin. Studies of early life seizures produced by either flurothyl exposure or kainic acid administration have found that they result in impaired learning and memory in adulthood. Mouse models of tuberous sclerosis (both TSC1 and TSC2) have been found to manifest learning/memory impairments, autistic-like features and epilepsy, and rapamycin treatment was found to improve both the seizures and comorbidities. Three other new transgenic mouse models were also identified with comorbid epilepsy and autism (BDNF over-expressing, CNTNAP2 deficient and oxytocin deficient mice).

Several of these studies specifically addressed the issue of potential mechanisms. In the lithium-pilocarpine model of TLE, HPA axis dysfunction, enhanced interleukin-1β signaling, and alterations in both pre- and post-synaptic serotonin receptor 1A receptors in the hippocampus have been identified as potential mechanisms contributing to the depressive phenotype in these animals. Studies of early life seizures produced by either flurothyl exposure or kainic acid administration have found that they result in impaired learning and memory in adulthood that is associated with alterations in LTP and LTD, and long-term molecular and structural changes, including altered NMDA receptor expression, impaired dendritic growth in hippocampal pyramidal neurons, and increased prefrontal cortical thickness. These models, and identification of some potential mechanisms underlying the behavioral and cognitive comorbidities they exhibit, should provide new opportunities to test potential approaches to the treatment of comorbidities.

Factors promoting or hindering progress

The most important factor contributing to the success of these studies was the increasing use of more sophisticated, sensitive, and well-validated measures of cognitive and behavioral co-morbidities in a wider array of animal models of epilepsy (e.g., for depression, the forced swim test, loss of sweet preference, decreased open-field investigation, and reduced dexamethasone suppression of cortisol; for psychosis, enhanced locomotor hyperactivity in response to amphetamine; for abnormalities in sociability, the social chamber test; for autistic-like behaviors, increased grooming; as well as a broader selection of measures of learning and memory). Other important factors were the development and identification of new transgenic mouse lines that have both spontaneous seizures and cognitive and behavioral comorbidities (Tsc1, Tsc2, BDNF over-expressing, CNTNAP2 deficient and oxytocin deficient mice for example), as well as GFP-expressing mice that permitted visualization of dendritic growth.

New or ongoing challenges and opportunities for research

There are a number of challenges that need to be met to further advance this area. These include:

- The development of more interdisciplinary or cross-disciplinary research teams/collaborators that include investigators with expertise in behavioral testing of rodent models.
- The development of endpoints (outcomes) that are measurable, reliable, and relevant to the human disease to further optimize preclinical models that are validated and resemble the human condition. For this we need to establish recommendations for tests to be performed for specific comorbidities and specific phenotypic criteria for each comorbidity.

- Improved technology, including more automated methods to test animals that are valid and are less time-intensive for researchers. We need to develop technology to permit *in vivo* monitoring of biomarkers relevant to comorbidity prediction, progression, and treatment response.

B. Identify predictors and underlying mechanisms that contribute to comorbidities.

3. Develop and implement a standardized protocol for screening pharmacologic and non-pharmacologic treatments of epilepsy for their amelioration or exacerbation of neuropsychiatric and cognitive co-morbidities.

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Summary of key advances

This benchmark includes the development of screening methods to determine who may benefit from a particular treatment for epilepsy (including not only antiepileptic drugs (AEDs) but also techniques like vagal nerve stimulation (VNS), deep brain stimulation (DBS), or surgical resection). This area also involves general studies to determine potential risks and benefits associated with such treatments and the possible interplay of patient characteristics with the general risks of interventions. (Factors such as age, baseline function, and comorbid diseases may modify risk/benefit calculations for any given treatment.)

In terms of AEDs, advances in our knowledge of the side effects of these drugs appears slower in recent years than during prior decades. Recent studies have focused on determining whether there may be increased risk of suicidality associated with specific AEDs and exploring the cognitive side effects of topiramate in particular, which can have a more deleterious impact on functioning in a subset of patients as compared to some of the other commonly used AEDs. One recent study showed that there are dose-related differences in topiramate and that brief assessment of patients can identify who is at risk of poor cognitive functioning on this medication by 6 weeks post-administration. This should be seen as a methodological advance that could be applied more generally to examining other AEDs. With regard to surgical intervention (also see Benchmark III.B.5), evidence is emerging that there may be previously unrecognized deficits in many patients undergoing temporal lobe (TL) resection for the control of seizures. Moreover, in addition to some of the known risks for increased post-surgical dysfunction (e.g., intact brain function, later age of seizure onset, normal neuroimaging), it appears that TL patients with extemporal or bitemporal damage on MRI may be at the greatest risk of decline. Patterns of fMRI results may be beneficial for predicting some aspects of cognitive decline following surgery. DTI findings may also add to prediction of decline in some areas (e.g., DTI data can be used to predict visual-field cuts following TL resection). With studies showing that the majority of new onset epilepsy patients already exhibit baseline cognitive deficits, there has been a call to screen patients at baseline to be able to assess progression and the impact of treatment. Finally, some quick screening methods have been developed during the last decade to explore side effects related to AED use.

New or ongoing challenges and opportunities for research

With regard to understanding the lack of recent studies exploring cognitive/behavioral comorbidities of AEDs, it appears that less money is available from pharmaceutical companies, who funded many of the studies in earlier decades examining comorbidities associated with AEDs. Studies focused on all treatments need to include appropriate measures of ability and not just self-ratings of function. Exploration of the use of neuroimaging to predict outcome from surgical intervention needs greater development, as emerging studies in this area appear promising. Developing baseline screening tools and establishing clinical standards for tracking behavioral functioning over time would be useful, as studies suggest that the adverse impact of AEDs can be determined rapidly, allowing for more appropriate treatment alterations. Recognizing when significant compromise of cognitive and/or behavioral function is starting to occur will also be useful for optimizing function in individual patients.

B. Identify predictors and underlying mechanisms that contribute to comorbidities.

4. Determine contributions of epileptogenesis, seizures, interictal epileptiform events, and homeostatic protective processes to the development of comorbidities.

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Summary of key advances

Intellectual Disability (ID) and Autism Spectrum Disorder (ASD):
In clinical studies, pediatric epilepsy was associated with intellectual disability (ID) in 25% of patients in the largest population-based, NIH-funded study encompassing greater than 10 years of follow-up. In a large population-based Swedish study, the lumped effects of CNS hemorrhage, edema, and seizures were linked to the development of later autism in pre-term infants. Rates of learning difficulties in pediatric epilepsy without ID were 41-62%. In a meta-analysis of 2,112 children with ASD, 21% had epilepsy with ID while 8% had epilepsy without ID. A true population based study from the UK estimated the overall incidence of epilepsy with ASD to be 10%.

Other comorbidities:
Depression was frequently reported in pediatric and adult cohorts with epilepsy and has led to a consensus statement on recognition and treatment. A population-based study from Canada found that while juvenile myoclonic (JME) may not require life-long medication in up to a third of patients, this disorder is associated with life-long depression, social isolation, unemployment, and social impulsiveness.

Ictal/Interictal discharges:
Data were reviewed regarding the relationship of continuous spike-waves during slow-wave sleep (CSWS) and Landau-Kleffner syndrome (LKS), two clinical epileptic syndromes that are associated with the EEG pattern of electrical status epilepticus during slow wave sleep (ESES), and regarding the overlapping behavioral phenotypes of these disorders with autistic regression. The differences in age of regression, degree and type of regression, and frequency of epilepsy and EEG abnormalities suggest that these are distinct phenotypes with implications for pathophysiology and treatment. In support of data suggesting that absence epilepsies are not benign, in a prospective, well-powered study involving assessment of sibling controls, abnormalities in language, processing speed, verbal memory and learning, and attention/executive/construction were found at the onset of idiopathic generalized and symptomatic/cryptogenic epilepsies (but not with idiopathic localization related epilepsies). This study involved children with normal IQ, which was thought to eliminate the potential confound of including children with the catastrophic epilepsies of very early childhood. In this study, epileptiform abnormalities on the EEG were predictive of neuropsychological deficits, suggesting a role of interictal discharges. The authors suggest the findings are consistent with a deleterious role of seizures.

Genetics:
Several genomic micro-deletions and micro-duplications have been reported to associate epilepsy with ASD or ID. These have been recently associated, where possible, with defective function in bicarbonate transporters, Na+/H+ exchangers, nicotinic acethylcholine receptors, contactin associated protein 2, microtubule associated protein tau, oligophrenin, protocadherin, actin-mediated clustering of GABA receptors (ARHGEF9 and Na/K/ATPase, and X-linked factors controlling transcriptional modification (JARID1C). Cyclin-dependent kinase-like 5 (CDKL5, Xp22) mutations, have been linked to a broad phenotype ranging from severe epileptic encephalopathy to seizures with Rett-like features in females as well as males.

Animal models – long-term effects:
Using the GAERS model of absence epilepsy which develops seizures later in life, behavioral abnormalities of depression and anxiety were independent of seizure onset, suggesting seizure onset at this point in development did not modify this comorbidity. In a rat model of neonatal seizures, seizures were independently associated with abnormalities in hippocampal dependent short-term memory. Kindling in adult rats was either associated with behavioral abnormalities or not, depending on the region and method of kindling. In a rodent model of prolonged (severe) febrile seizures, MRI imaging abnormalities after the seizure correlated with later abnormal cognitive function. Multiple flurothyl-induced early-life seizures (ELS) lead to alterations in behavior. This is associated with altered connectivity assayed with alterations of dynamic signal processing. While the behavior can be improved with training, the alterations in connectivity persist. Alterations in connectivity following ELS represent a persistent biomarker of prior seizure history. In an important negative study, an animal model of TLE in rodent mothers suggested that maternal epilepsy may not be detrimental to the developing rodent fetus. However, another study came to a different conclusion.

Treatment effects in animal models:
In mouse models of tuberous sclerosis, rapamycin treatment showed some functional benefits but did not prevent or modify dysplasia. In a rodent model of absence epilepsy, treatment with ethosuximide that prevented spike-wave discharges improved measures of depression. Equally important, early treatment appeared to ameliorate epileptogenesis in this model. Hypoxia-induced early life seizures (HI-ELS) are associated with immediate, time-limited activation of proteins associated with the mTOR pathway. Treatment with the mTOR inhibitor rapamycin prior to HI-ELS attenuates this and later development of epileptiform disturbances and abnormalities in social memory. Activation of the mTOR pathway in HI-ELS may underlie later outcomes, but their time-limited activation makes clinical application of rapamycin less feasible. Single-dose rapamycin negatively impacts behavior in normal rats. Treatment with glutamate receptor antagonists are also helpful in this model. The WAG/Rij rat was treated with aripiprazole, and improvement was noted in seizures and depressive behavior suggesting that absence seizures and depressive behaviors are both causally and therapeutically linked.

<u>New or ongoing challenges and opportunities for research</u>
Ongoing challenges in the comorbid conditions will likely focus on therapeutic options that treat seizures without confounding symptoms associated with the accompanying disorder. In ideal situations, both symptoms are controlled through medical intervention. As mentioned above, pediatric epilepsies are commonly associated with ID and ASDs. A key factor that is both a challenge and an opportunity for research is finding a therapeutic option that does not exacerbate abnormalities in cognition and working memory. Therefore treatment trials of mTOR inhibitors are promising in that both seizures and social memory abnormalities are controlled. Additional challenges concern the timing for which certain treatments will be most effective. When dealing with neurodevelopmental disorders such as ASDs and ID, it is not always known if postnatal changes in brain development will alter therapeutic options. An opportunity for scientists who study neurodevelopmental disorders is determining *when* abnormalities in ion channels and synaptic efficacy occur in addition to *how* these abnormalities affect brain function. Therefore a key challenge for this benchmark will be to tackle multiple sources of disruptive symptoms that occur throughout early developmental changes in pediatric epilepsies.

B. Identify predictors and underlying mechanisms that contribute to comorbidities.

5. Determine if the affective, attentional, and cognitive disorders in people with epilepsy are the same as those in people without epilepsy with respect to natural history, presentation, treatment and underlying mechanisms.

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Summary of key advances

A number of new studies have examined cognitive/behavioral differences between epilepsy syndromes and healthy comparison subjects. For example, there have been some NIH-funded studies examining cognitive/behavioral deficits in patients with benign childhood epilepsy with centrotemporal spikes (BECTS), and others demonstrating that behavioral issues are often present before the onset of epilepsy in children in general. A few studies have examined epilepsy patients in relation to other populations (e.g., showing that psychopharmacological treatments work as well for patients with epilepsy and ADHD as for patients with ADHD only). We likely know the most about the cognitive/behavioral profiles of temporal lobe epilepsy (TLE) patients. However, new studies have revealed many previously unrecognized areas of dysfunction in these patients (involving language, object recognition, semantic learning, and aspects of affective and social processing), both before and after surgery. These deficits are not routinely examined in clinical practice yet appear to have a profound negative impact on daily function. Research is demonstrating more precise relationships between neuroanatomical subregions of the TLs and different aspects of memory and learning. Such studies suggest that many standard clinical measures of cognition may not adequately capture functions of interest. The use of functional neuroimaging measures of connectivity (e.g., DTI, resting state fMRI, MEG) and statistical methods for modeling network behavior (e.g., graph theory) are revealing new insights into the neural underpinning of brain functions in general, and how they are impacted by seizures (including reorganization of function as well as the occurrence of deficits). Finally, the NIH toolbox has been expanded to the assessment of epilepsy (The Epilepsy Common Data Elements – see **http://www.commondataelements.ninds.nih.gov/Epilepsy.aspx**) , providing a minimum set of tests that should allow for easier comparison across studies conducted in different centers.

New or ongoing challenges and opportunities for research

Many studies have been small in scope, lack thorough measures of relevant functions, and rely on cross-sectional rather than prospective, longitudinal methods. In studies demonstrating common patterns of dysfunction in epilepsy syndromes, uncertainty remains over whether deficits resolve with management or resolution of seizures. There are still many syndromes, including focal epilepsies involving extratemporal brain regions, where existing research is scant, and few studies have examined epilepsy in relation to other relevant patient groups. Measures used in many of these studies have been general in nature, and leave a lot of unexplored areas where greater parcellation of function is required. In addition, evidence of previously unrecognized deficits really represents a new area of study, and little is known about possible progression of deficits in these areas or effective treatment options. There are virtually no studies exploring rehabilitation of deficits in TLE patients (or other epilepsy syndromes), and therefore no knowledge of whether research completed in other disease areas might apply. There are also obvious holes in our clinical measures that need to be addressed in order to assess relevant functions. In the area of surgery, much work is needed to determine if the surgical approach can be altered to avoid more recently recognized types of deficits, or whether patients at risk of decline can be predicted. Barriers to overcome include the need to pool data across centers to achieve adequate statistical power (such as in the case of most focal epilepsy syndrome apart from TLE), and the need to implement core measures. As many of the promising tools and methods are relatively new (e.g., DTI analysis, resting state analysis, network modeling), more work is required to develop these tools and extend their use to epilepsy as well.

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

1. **Determine whether the treatments used for at least two of these conditions in isolation are effective when utilized in people with epilepsy or if these co-morbidities require different strategies.**
2. **Develop at least one efficacious care model for the diagnosis and treatment of epilepsy and validate that it improves the outcomes for patients with co-morbidities.**

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Summary of key advances

Epidemiologic studies have demonstrated that psychiatric comorbidities are relatively frequent in patients with epilepsy (PWE), with life-time prevalence rates averaging 35% for a psychiatric disorder. In adults, depression and anxiety disorders are the two most frequent psychiatric comorbidities, while Attention Deficit Hyperactivity Disorders (ADHD) is the most frequently identified psychiatric comorbidity in pediatric patients, though depression and anxiety disorders have been recognized more frequently in this age group. Psychotic disorders are the least frequent psychiatric comorbidity in PWE, but their prevalence is higher than in the general population.

Yet, despite their relatively high prevalence in PWE, little data are available on the treatment of these psychiatric comorbidities. For example, since 2007, there has been only one randomized controlled study that compared the efficacy of sertraline, a selective serotonin-reuptake inhibitor (SSRI) and cognitive behavioral therapy (CBT) in the management of major depressive episodes (MDE) in PWE. Symptom remission was found in 60% of patients in each treatment arm. There was a second controlled study on the treatment of depression in PWE, to assess the impact of a six-week group CBT on seizure frequency and changes in mood and psychosocial well-being in 37 elderly patients with epilepsy aged 60 years and older. Patients were randomized to receive group CBT or be part of a control group. Measures of depression, dysthymia, psychosocial functioning, and seizure frequency were recorded at baseline and at the end of the intervention. Seizure frequency was significantly reduced in the CBT group compared to the control group. The CBT and control groups improved significantly from baseline and there were no significant group differences on measures of depression and psychosocial functioning.

No controlled data on the treatment of anxiety disorders, ADHD, and psychotic disorders are available for PWE. Thus, in the absence of any controlled trials, two groups of experts generated consensus statements on the treatment of psychiatric comorbidities in epilepsy and concluded that the treatment used in primary psychiatric disorders is applicable to that of psychiatric comorbidities afflicting PWE. Yet, it should be emphasized that these recommendations are based on “expert experience” and not on controlled data.

New or ongoing challenges and opportunities for research

Many questions remain unanswered. For example, depressive disorders in PWE present with atypical clinical manifestations that are often pleomorphic and encompass symptoms of anxiety, irritability, and pain in addition to the depressive symptoms. While open trials have suggested that pharmacotherapy with SSRIs can be effective, their efficacy has yet to be established. Postictal depressive and anxiety episodes are relatively frequent in patients with treatment-resistant epilepsy with median duration of 24 hours, but which may last up to 7 days. Yet, there are no data on whether psychotropic drugs are effective in the treatment of these types of episodes.

In the case of ADHD, “experts” have suggested that the use of CNS stimulants should yield comparable efficacy to that seen in primary ADHD, while antipsychotic drugs are recommended for interictal and postictal psychotic episodes. Psychotic disorders are considered to have a more benign course in PWE and hence should be expected to respond to

lower doses of antipsychotic medication than those used in primary psychotic disorders; yet, whether such is the case is yet to be established.

With respect to safety, there is consensus that antidepressant drugs of the SSRI and serotonin norepinephrine reuptake inhibitor (SNRI) are safe when used at therapeutic doses, but can lead to seizures in cases of overdoses or very high serum concentrations. However, there are no data on the efficacy and safety of the newer families of antidepressant drugs (e.g., mirtazapine) in PWE. Furthermore, controversies persist on the safety of CNS stimulants in children with ADHD and epilepsy. This question can only be answered with a placebo-controlled trial, as there is a bidirectional relation between ADHD and epilepsy.

In summary, there is a lack of data supported by high quality evidence for the treatment of psychiatric comorbidities in PWE. Randomized placebo-controlled trials are needed to determine the efficacy of pharmacologic treatments and CBT for the various psychiatric disorders in these patients.

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

3. Develop and validate novel treatments and management strategies for cognitive and neuropsychiatric disorders of people with epilepsy that are not adequately treated with currently available therapies.

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Summary of key advances

The primary progress has been to demonstrate preliminary efficacy of a number of existing treatments when applied to persons with epilepsy (PWE). Although these treatments are not necessarily highly novel, it is not yet clear that PWE require treatments that are substantially different from those proven to be effective in other populations. A number of studies in persons with epilepsy (PWE) have demonstrated the efficacy of focused, short-term, behavioral approaches to disease-self-management and treatment of mood disorders. These treatments can be delivered in a number of modalities, including over the phone or the internet, enhancing the potential for accessible and cost-effective treatment. Studies of established pharmacologic treatments have shown efficacy in treating mood disorders and attention-deficit hyperactivity disorder in PWE. Results of these and other studies were summarized in a report by the ILAE Commission on the Neuropsychiatric Aspects of Epilepsy that provided consensus, evidence- and practice-based statements to guide the management of these conditions. More limited progress has been made in the treatment of memory and other cognitive problems in PWE, with several small-scale pilot studies showing some promise of memory training and psycho-educational approaches.

Factors promoting or hindering progress

Although the studies that have been conducted show promise, the ILAE commission acknowledged that many of their statements on management represented expert opinion only, given the dearth of high-quality studies. Fear of provoking seizures continues to be a barrier to the use of anti-depressants and stimulants in PWE. The studies to date have had insufficient power and duration of follow-up to provide sufficiently reliable estimates of this risk. There also appears to be very limited information about the perceived trade-offs between seizure exacerbation and symptom relief among PWE, physicians and care-givers. Fear of provoking seizures seems to be greatest among clinicians with less experience treating PWE (e.g., primary care physicians and psychiatrists, as opposed to neurologists). The stigma of mental health treatment also may compound stigma experienced by PWE and may further limit their willingness to seek treatment

New or ongoing challenges and opportunities for research

Opportunities exist for collaboration of investigators to conduct large, simple trials of combined pharmacologic and behavioral treatments powered to detect clinically meaningful differences in the risk of seizure exacerbation and impact on mood. Efficacious, self-management strategies might fruitfully be combined with these approaches to maximize adherence and treatment effectiveness. Similar studies are needed for emerging treatments for memory disorders in this population. There are continued opportunities and challenges to educate PWE and caregivers about the importance of screening and early treatment with therapies currently established for mood disorders in general.

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

1. Sudden unexplained (or unexpected) death in epilepsy (SUDEP).

a. Develop and validate at least one prevention strategy to decrease the occurrence of SUDEP.

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Summary of key advances

Although preventative strategies are undergoing study, none has been validated. However, sufficient evidence has accrued to putatively consider the control of generalized convulsive seizures as one measure in reducing SUDEP risk. SUDEP prevention strategies are not currently targeted at specific mechanisms because the agonal pathophysiological mechanisms are still unclear (also see Benchmark IIID3). A significant body of evidence now suggests that there is cardiac and/or respiratory dysfunction with seizures and particularly with generalized tonic-clonic seizures, the seizure type that is most frequently associated with SUDEP. In part driven by the Sudden Infant Death Syndrome (SIDS) story, there has been significant interest in serotonergic mechanisms as a possible candidate neurotransmitter system involved in SUDEP pathogenesis, thus opening up a potential avenue to a preventive strategy.

Affirming clinical risk factors and at-risk population:

The leading experts of the Task Force on Epidemiology of the International League Against Epilepsy performed a meta-analysis of four major case-control studies and defined consistent clinical risk factors for SUDEP: longer (>15 years) duration of epilepsy, presence of idiopathic/cryptogenic epilepsy, frequent generalized tonic-clonic seizures, polytherapy, male gender, age below 60 years. Although SUDEP is considered exceedingly rare in the pediatric population, there is emerging evidence that children with severe myoclonic epilepsy of infancy (SMEI) are at increased risk for SUDEP. We need more and better data on population-based SUDEP epidemiology in different geographic and demographic settings. Such an initiative was recently begun by the CDC. Accomplishment of this goal will allow for the definition of epidemiological SUDEP risk factors that may be amenable to rapid intervention, and thus prevention of SUDEP.

The serotonin (5HT) theory and SSRI intervention:

Serotonin is thought to enhance respiration in response to hypercarbia, which can occur during generalized tonic-clonic seizures in humans. Several studies of SIDS brains point to a 5HT link. Mice with an audiogenic seizure disorder due to a genetic deletion of the $5HT_{2c}$ receptor die in the post-ictal period if unresuscitated. DBA/2 strain mice, which suffer audiogenic seizures, have marked susceptibility to post-ictal respiratory arrest, which can be reduced when pre-treated with selective serotonin re-uptake inhibitors (SSRIs). Semichronic administration of a selective serotonin reuptake inhibitor (SSRI) appears to prevent seizure-induced sudden death in a mouse model of SUDEP. When fluoxetine was administered acutely or semichronically, it significantly reduced incidences of respiratory arrest, appearing to support a previous report on the effects of SSRIs on respiration in patients with epilepsy. In a retrospective study that examined video-telemetry data of 496 seizures from 73 patients with focal epilepsy, SSRIs were associated with reduced likelihood of ictal oxygen desaturation in partial seizures. However, SUDEP is most often associated with generalized convulsions, and further work in a larger group of patients is required.

The electrocecerebral shutdown theory and risk identification:

A case-control study found that prolonged EEG suppression beyond 50 seconds and below 10 microvolts in the post-ictal period after a generalized motor seizure appeared to identify patients at risk of SUDEP. A subsequent study using similar methodology did not find an association, although differences in the patient populations studied and choice of controls may bias comparisons. In another study, custom-built wrist-worn sensors were used to continuously record sympathetically mediated electrodermal activity (EDA) of patients with refractory epilepsy admitted to a long-term video-EEG monitoring unit. Increases in the EDA response amplitude correlated with an increase in the duration of post-

ictal EEG suppression, pointing to a potential autonomic correlate of prolonged post-ictal EEG suppression. Validation of both EDA amplitudes and EEG suppression in large cohort studies may lead to better identification of high risk individuals, and to appropriately heightened supervision of these patients and emphasis on strict medication compliance as a generic SUDEP prevention strategy.

The seizure/apnea alert approach:
Several devices have been patented that are designed to alert caregivers to the occurrence of a seizure, thus potentially leading to early, lifesaving intervention. One approach by British investigators and in the early stages of development has been to develop a miniaturized, wearable apnea alert device that detects the noise of respiration in epilepsy patients. Other approaches have used motion detection alarm systems. None have as yet reached a stage of large-scale evidence-based use.

Factors promoting or hindering progress
Funding by NIH, non-profit lay and professional organizations, and the CDC resulted in new opportunities for research on SUDEP. The NIH/NINDS initiative for SUDEP funding has resulted in two P20 planning grant awards toward a potential Epilepsy Center without Walls focused on SUDEP. Both projects, using different approaches, emphasize identification of risk factors that will hopefully lead to prevention screening and a more targeted approach to preventing SUDEP. Investment in SUDEP research and the prevalent enthusiasm and energy amongst SUDEP researchers are likely to be key factors in furthering knowledge.

New or ongoing challenges and opportunities for research
Challenges are that suspected risk factors and pathophysiologic mechanisms are very difficult to prove because of the unpredictable occurrence of SUDEP, which is mostly in the community setting distant from investigating centers, and the low rate of complete autopsies. Opportunities exist in focusing on large prospective cohorts of high-risk patients for validating preventative strategies. The use of SSRIs in post-ictal respiratory compromise in humans requires larger scale evaluation, although the only human evidence for a possible role is weak. However, as animal data accrues, the case for human studies will continue to build. Any outcomes-based, practical evaluation of such pharmacological intervention has to be of a large scale, given the low incidence of SUDEP, and must employ a multi-modal physiological data driven approach that incorporates the use and study of a variety of signal parameters. The alert devices approach poses a different kind of challenge in which an evidence base is difficult, both in terms of establishing efficacy in seizure detection as well proving a difference in SUDEP mortality outcomes. The research community also needs to continue fostering partnerships with the public in the mission to combat SUDEP. The SUDEP Coalition is in the forefront of this effort, and the Partners Against Mortality in Epilepsy Conference (PAME) meeting highlighted the importance of broad communication and dissemination of knowledge to professional and lay communities.

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

2. Sleep Disturbances

a. Identify the range and frequency of sleep disorder subtypes associated with epilepsy.
b. Identify the influence of sleep disorders on the incidence of seizures.
c. Identify the influence of sleep disorders on at least one comorbidity of epilepsy.

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Summary of key advances

The goals of this Benchmark have been partially met. Key advances include: (A) Further characterization of sleep disorder subtypes and therapy, specifically obstructive sleep apnea syndrome (OSAS) and the effectiveness of interventions such as CPAP, by several retrospective reviews and smaller prospective studies. (B) Improved tracking of seizures in relationship to sleep and wakefulness, which allowed further identification of day and night time patterns of seizures and related sleep disorders, providing potential biomarkers for seizure prediction. This facilitated novel treatment paradigms with medication dosing at times of greatest seizure susceptibility. (C) Lastly, investigations of sleep-dependence of behavioral comorbidities, memory and cognitive dysfunction in epilepsy patients; i.e. in studies on sleep-potentiated spiking and electrical status epilepticus in sleep.

Factors promoting or hindering progress

Improved seizure and sleep tracking devices, such as electronic seizure diaries or portable sensors, as well as improved signal processing of video-EEG data, sleep studies, heart rate, breathing and other biomarkers, such as actigraphy or skin conductance, have all facilitated the research. Support for research on obstructive sleep apnea in epilepsy has also spurred the progress. A future catalyst for research in this area may be the NeuroNEXT initiative (NINDS-funded Network for Excellence in Neuroscience Clinical Trials). The NeuroNEXT infrastructure consists of 25 clinical centers across the US, a central clinical coordinating center, and a central data coordinating center. Investigators who have an idea for a phase 2 trial or biomarker study, but who might not have experience of running such studies or access to enough patients, can apply to use this infrastructure.

New or ongoing challenges and opportunities for research

Large well-designed prospective studies are rare. One unmet need is that most studies thus far have focused on OSAS, and not on other sleep disorders such as circadian rhythm disorders, daytime somnolence, abnormal sleep-related movements, and parasomnias, especially in children. The challenge ahead is to improve the quality of data with additional details on sleep disorders and circadian rhythms. Portable seizure and sleep tracking systems are a first step towards recording better sleep and epilepsy data. Combined research in epilepsy and sleep will offer novel diagnostic and therapeutic management options. Knowledge of the interactions between circadian periodicity, entrainment, sleep patterns, disrupted sleep structure and epilepsy may provide additional diagnostic options and novel insights into the physiologic, biochemical, and genetic regulation processes of epilepsy and the circadian clock, rendering new treatment options possible. Temporal fluctuations of seizure susceptibility based on sleep homeostasis and circadian phase may provide predictability based on mathematical models in selected epilepsies. Chrono-epileptology (the science of the timing of seizures and related treatment options) offers opportunities for individualized patient-oriented treatment paradigms based on chrono-pharmacology, differential medication dosing, prediction modeling, chrono-drug delivery systems, and utilization of "zeitgebers" such as chronobiotics. The current benchmark acknowledges the importance of understanding the effects of sleep on epilepsy, and of epilepsy on sleep and related comorbidities, but further advances in chrono-epileptology will undoubtedly offer individualized, targeted paradigms for seizure control.

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

3. SUDEP

a. Identify the mechanisms responsible for SUDEP (including effects of seizures on autonomic functioning, particularly cardiac and respiratory).

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Summary of key advances

In the past five years, there have been important discoveries and research efforts that considerably improved our understanding of potential SUDEP mechanisms. There has been unprecedented cross-talk between basic and clinical research resulting in rapid translation of bench science discoveries into clinical investigations, preliminary screening of candidate mechanisms and molecular risk factors (e.g., autonomic function screen and long QT gene screens), and testing of potential preventative interventions (i.e. serotonin re-uptake inhibitors (SSRIs) in patients with epilepsy). The key advancements that accelerated our search for solutions in SUDEP occurred in the following areas. (Also see Benchmark IIID1.)

Basic and translational research made important contributions towards unraveling SUDEP mechanisms and risk factors. Research hypothesis and investigational efforts have focused on exploring neuro-cardiac, autonomic, and respiratory compromise as candidate mechanisms in SUDEP. Epilepsy has been observed in a mouse model with mutations in a gene that causes sudden cardiac death in humans. 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. Some SUDEP animal model research studies have explored the changes in autonomic nervous system function, while other investigations looked at the potential role for over-activation of adenosine receptors after seizures and the administration of caffeine as a potential preventive intervention. It became apparent that the serotonin system has an important role in seizure generation, breathing, arousal, and in sudden death in animal models and humans. Serotonin reuptake inhibitors offer an interesting and immediately available intervention that could potentially ameliorate hypoxia triggered SUDEP risk. Recently, a primate colony emerged as an interesting model system to study the natural incidence, course, and outcome of primary generalized epilepsy including SUDEP.

Hypotheses and discoveries in basic science were invaluable in informing the clinical research of SUDEP and identification of potential high risk patient population.

- *Respiratory hypothesis:* Systematic and comprehensive respirometry of monitored epilepsy patients documented frequent and potentially severe and prolonged peri-ictal hypoxia in patients with temporal lobe epilepsy. The degree of ictal oxygen desaturation in partial seizures of patients chronically exposed to SSRIs was decreased as compared to patients not taking SSRIs. Moreover, ictal hypoxemia was frequently associated with cardiac repolarization abnormalities.
- *Cardiac arrhythmias hypothesis:* The discovery of candidate molecular risk factors (LQT and HCN pacemaker genes) in basic translational research was applied in a retrospective postmortem screen of SUDEP samples. While the human investigations did not prove causality, they did underscore the importance of focused and systematic research on genomic variation in a candidate gene set in well-defined SUDEP cases. There is also mounting evidence that dysfunction in autonomic control plays a role in epilepsy-related cardiac arrhythmias in adults and children with epilepsy.
- The mechanisms of the post-ictal electro-cerebral suppression and that of the electro-cerebral shutdown and their contribution to SUDEP remain to be elucidated.

Factors promoting or hindering progress

- *SUDEP Task Force:* In 2007, the American Epilepsy Society and the Epilepsy Foundation formed a task force to address the research and educational issues concerning the phenomenon of SUDEP. Among the published recommendations of the task force was that there should be a multidisciplinary workshop on SUDEP.

- *An NINDS sponsored workshop* was convened in November 2008. The workshop played a key role in defining the state of SUDEP mechanistic understanding, research trends, needs, and gaps in knowledge. It was critically instrumental in raising SUDEP awareness, bringing research funding, and speeding up discoveries in the field of SUDEP. Following the NINDS SUDEP Workshop in 2008, the SUDEP Coalition was formed to harness and coordinate the SUDEP-related activities of organizations such as AES, CDC, CURE, EF, ETP/FACES, NINDS, and SUDEP Aware.
- *Research funding:* The major scientific breakthroughs in our understanding of SUDEP mechanisms could not have happened without focused SUDEP-oriented support from non-profit organizations and governmental agencies. This support, including planning grants for a potential SUDEP Center Without Walls, has enabled funding for SUDEP research by established investigators and has attracted new basic scientists and physician scientists.
- *Partners Against Mortality in Epilepsy Conference - PAME (June 22-24, Evanston, IL).* This was the first-of-its-kind three-day conference devoted to SUDEP, where clinical, basic science and patient/family participants came together to educate and support each other about SUDEP. The meeting was a key project of the SUDEP Coalition and its participating organizations.
- *SUDEP Registries:*
    - *STOP SUDEP Tissue Donation Program* –SUDEP registry and tissue bio-repository with active recruitment and associated genomic analysis
    - *North American SUDEP Registry* – SUDEP registry

<u>New or ongoing challenges and opportunities for research</u>

There is a continued need for the integration of hypothesis-driven SUDEP research to define molecular predictors, biomarkers, diagnostic screening paradigms, and translation into clinical science. Studies in patients at high risk for SUDEP and the development of preventative strategies for them are important, because we are continuing to lose patients to SUDEP. Efforts focused on systematic case registry, tissue banking, and development of paradigms for information and tissue sharing will remain important in understanding and stopping SUDEP. New analytical platforms will certainly be important as well in future discoveries of new SUDEP candidate genes. Finally, career development for researchers interested in SUDEP will be needed for uninterrupted progress.

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

4. Identify optimal strategies to avoid systemic disorders associated with epilepsy and its treatment (e.g., osteopenia, endocrine disturbances, reproductive disorders, and teratogenicity).

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Summary of key advances

The goals have been met for avoidance of adverse pregnancy course and outcome, and the teratogenicity risk associated with some antiepileptic drugs. Many of these strategies have become the standard of practice in women with epilepsy. For the condition of osteopenia, the goal is only partially met.

Understanding how to treat pregnant women with epilepsy and the impact of antiepileptic drug *in utero* exposure is integral to the care of women with epilepsy and has received much study in this time period. 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. Emerging data from multiple hospital- and population-based registries better defined the risk of teratogenic effects of antiepileptic drugs. Valproate is consistently associated with an increased risk of major congenital malformations, and studies suggest a specific increased risk of neural tube defects. Carbamazepine may also increase the risk of neural tubes defects, but this is not a consistent finding. Topiramate increases the risk of oral clefts as demonstrated in multiple studies. The FDA has classified it as a class D drug in pregnancy (known effects on the developing fetus). Levetiracetam appears to have a lower risk of major congenital malformations than other antiepileptic drugs. Higher antiepileptic drug doses are associated with an increased risk of major congenital malformations. The NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study enrolled pregnant women with epilepsy who were taking a single antiepileptic agent and prospectively evaluated cognitive outcomes among children exposed to different antiepileptic drugs (carbamazepine, phenytoin, lamotrigine, valproate) *in utero*. Cognitive data at 3 and 4.5 years found adverse effects of valproate exposure on cognitive function, particularly verbal abilities. Motor, adaptive, and emotional behavioral functioning was impaired in the 4 studied antiepileptic drug groups with dose response effects seen with both valproate and carbamazepine. Breastfeeding did not affect cognitive outcomes of the studied children. Further research efforts should focus on increasing our understanding of the effects of all available antiepileptic drugs on the anatomic and neuropsychological outcomes of children exposed to these agents *in utero,* as well as on other pregnancy outcomes including rates of caesarian sections and rates of low birth weight.

Although bone health problems including increased fracture risk have been reported in people with epilepsy, it remains unclear whether they are due to antiepileptic drug exposure which could adversely affect bone metabolism, or whether they are related to other factors such as poor general health, co-occurring medical conditions, genetic predisposition, neuromuscular impairments, or lifestyle behaviors. Cytochrome P450 enzyme inducing antiepileptic drugs are most consistently associated with adverse effects on bone such as low bone mineral density and alterations in bone turnover markers. Some reports, however, do not find a negative effect of carbamazepine on bone and others find that non-enzyme inducing antiepileptic drugs adversely affect bone. Further study needs to be done to better define why persons with epilepsy are at increased risk of bone health problems and should focus on potential mechanisms as well as screening and treatment options.

Despite studies suggesting that persons with epilepsy have increased rates of infertility and other endocrine disturbances, there has been limited study to further our understanding on the prevalence and potential mechanisms to explain these findings.

New or ongoing challenges and opportunities for research

Large-scale prospective registries to follow women with epilepsy during their pregnancies, and also providing long-term periodic assessment of their children (e.g., the NEAD study) have promoted progress in our understanding of these

issues. However, the success of studies to meet these goals is heavily dependent on patients' behavior and life-style, making these studies extremely difficult to complete.

For these goals to be accomplished, both observational and intervention studies require long-term follow-up of patients, which is expensive though necessary to conduct. Opportunities and unmet needs include: 1) More research efforts focused on increasing our understanding of the effects of all available antiepileptic drugs on children exposed *in utero,* as well as on other pregnancy outcomes; 2) More studies to determine how some antiepileptic drugs affect bone metabolism, and which therapeutic intervention is effective in restoring bone health.

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

1. **Determine the types and frequency of NES in the general population and in people with epilepsy.**
2. **Identify common susceptibility factors and etiologies for NES.**
3. **Validate at least one effective treatment for NES.**

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Summary of key advances

Goals have been partially met for these benchmarks. Key advances include:

- *NES diagnosis:* a study examined video-EEG inter-rater reliability (IRR) providing video-EEG raters access to all recorded seizures and history for each patient and found that agreement was 'nearly perfect'. This study highlights that video-EEG interpretation is, indeed, the gold-standard diagnostic test for NES when video-EEG interpretation incorporates the clinical picture.
- *NES epidemiology:* a full scale US population-based study devoted to NES surveillance has not yet been conducted. Another study, however, identified significant NES needs in the military, showing that NES occurs in 25% of the veteran population with seizures, occurring at similar rates to the civilian population. A few population studies have generated data based on VEEG-confirmed diagnosis of NES, however these estimates are at best a lower bound of the true incidence/prevalence of NES in the general population. Even less data are available regarding the fraction of epilepsy patients with concomitant NES.
- *Susceptibility:* more studies published on psychological profiles and susceptibility factors in the NES population confirm a history of trauma and maladaptive coping resources as consistently characterizing patients with NES. Another study found that patients with NES can develop medically unexplained symptoms if underlying issues are not addressed in treatment.
- *Treatment:* three prospective pilot randomized controlled trials (RCT) have been completed for NES since the second Curing Epilepsy conference. An NINDS funded pilot pharmacologic RCT showed reduction in NES frequency in the medication arm and an increase in NES in the placebo arm (*NCT00159965*). A prospective pilot RCT revealed benefit from cognitive behavioral therapy (CBT) for NES with reduction in NES (*NCT00688727*). A multi-site pilot RCT for NES showed CBT for NES reduced NES and improved comorbid symptoms (*NCT00835627*).

Factors promoting or hindering progress

NINDS was the first NIH institute to support a pilot RCT for NES *(5K23 5NS45902)*. NINDS/NIMH/AES support for a multidisciplinary NES treatment workshop provided the necessary foundation to set NES Research Benchmarks. Following that, NES Task Forces were commissioned by the AES and the ILAE. Subsequent support from the Epilepsy Foundation and AES directed at NES treatments has promoted progress in NES intervention development. A major factor that promoted progress in this area is the appearance of a plethora of new literature in the past five years calling attention to NES as an often misdiagnosed epilepsy-mimic, and possibly a major public health problem. A major hindrance to progress in this area is lack of a known NES diagnostic test that is cost-effective, operator-independent, and can be performed in an outpatient setting. NES diagnosis is based on long-term VEEG monitoring, which is expensive and restricted to centers specializing in epilepsy care. Even more challenging is the task of identifying the frequency of NES in patients with epilepsy, which requires several days of inpatient VEEG monitoring to ascertain the diagnosis of NES and epilepsy in one setting.

New or ongoing challenges and opportunities for research

Of the 1% of the US population diagnosed with epilepsy, 5 to 20% actually have NES, making NES as common as Parkinson's disease or multiple sclerosis. Current estimates suggest that 10% of adults with NES also have epilepsy, and 30% of children with NES also have epilepsy. A population-based study for NES could formally establish the incidence and prevalence of NES and mixed NES/epilepsy. Risk factors for developing NES have been assessed from retrospective data. Precursors for NES are known to be traumatic events and developmental privation. A prospective trial following patients with known risk factors could better establish susceptibility factors and NES etiologies. A major unmet need in the research of NES is identification of biomarkers. This is a general problem with psychiatric illnesses (and epilepsy), and is not without ethical considerations (i.e., risk of labeling). A major opportunity for the advancement of knowledge in this area is that NES is unique to other psychogenic disorders in that the use of VEEG monitoring adds an element of scientific objectivity to the diagnosis of NES. This is unlike psychogenic movement disorders, psychogenic paralysis, or psychogenic pain syndromes, for example, in which diagnosis is made on clinical and phenomenological grounds. Controlled pilot treatment trials are revealing that CBT for NES can reduce seizure frequency and improve comorbid symptoms. A fully powered prospective RCT would provide definitive Class I data needed to provide the evidence base for NES treatments. Other unmet needs include, once class I data are provided, therapy dissemination to equip epilepsy center personnel with needed treatments for patients with NES. NeuroNEXT, the Epilepsy Phenome/Genome Project, Epi4K consortium, and the Epilepsy Center without Walls are all initiatives to promote networks of epilepsy research. Efforts focused on NES specifically, or efforts to add a comorbidities/NES focus to existing projects, would foster advances in research on the comorbidities of epilepsy and NES.