

## **Advances, needs, and opportunities in epilepsy research:**

*input from NINDS RFI and Epilepsy Research Benchmarks Stewards*

This compilation and summary integrates input provided by the Epilepsy Research Benchmarks Stewards in their [2007-2012 Progress Report](#) and received through a Request for Information (RFI) issued by NINDS in November 2012 ([NOT-NS-13-003](#)). Responses to the RFI were received from epilepsy researchers, people with epilepsy and their family members, other Federal agencies, professional and advocacy organizations, and anonymous individuals. The summary focuses on input related to biomedical research and is organized along current areas of the Epilepsy Research Benchmarks, though some topics may be relevant to multiple areas. In each area, “Goals” summarize overarching messages reflected in the input received, and research opportunities are presented as questions. *This summary is intended to inform discussions about updating the Epilepsy Research Benchmarks and does not represent the views of the NINDS or a proposal for new Benchmarks.*

### ***Benchmarks Area I: Prevent epilepsy and its progression.***

#### **Goals**

- Identify causes and risk factors for the epilepsies (including but not limited to genetic, autoimmune, or related to infections or brain injury from trauma, stroke, hypoxia/ischemia, or other insults).
- Understand the mechanisms of epileptogenesis following various types of insults to the brain.
- Translate knowledge about epileptogenic mechanisms into antiepileptogenic therapies targeting specific risk factors or causal mechanisms.

#### **Advances**

- Gene identification for rare epilepsy syndromes; recognition of role for CNVs in some epilepsies; identification of mutations in genes underlying epilepsy syndromes that fall into a more limited number of common molecular pathways
- Genetics advances also informing animal model development, translational research, and improvements in phenotyping
- Identification of autoimmune causes of epilepsy, pointing to potential for treatment based on immune modulation
- Evidence suggesting that alcohol consumption or fetal alcohol spectrum disorders associated with risk for epilepsy
- Identification of HHV-6B in subset of patients with status epilepticus and mesial temporal lobe epilepsy
- Movement away from hypothesis that epileptogenesis involves the same mechanisms as those responsible for acute seizures in the epileptic brain and beyond a focus on excitatory/inhibitory balance
- Insights into mechanisms of epileptogenesis: mTOR pathway signaling, inflammation, metabolic processes, blood-brain barrier compromise, depolarizing actions of GABA, disruptions in neuronal circuit development, and neuromodulatory processes
- Further understanding of role of astrocytes/astrogliosis in epilepsy, including in seizures associated with brain tumor (and potential treatment with sulfasalazine); promise of adenosine-based therapies
- Evidence that some epileptogenic mechanisms may be shared across multiple forms of epilepsy, e.g., mTOR pathway signaling in TSC and other forms of epilepsy
- New animal models developed for viral encephalitis, infantile spasms, and early epileptic encephalopathy
- Growing interest in epileptogenesis biomarker research

#### **However**

- There are no biomarkers or other means for predicting which individuals will develop epilepsy
- There are no interventions that can prevent epileptogenesis in those at risk

#### **Research questions and opportunities**

- Causes of/risk factors for epilepsy
  - o Which genetic associations determined to date can be functionally validated as contributing to epilepsy?
  - o What additional genetic variations contribute to epilepsy, including both rare syndromic and more common forms?
  - o What is the relationship between alcohol consumption and/or alcohol exposure in utero and the risk for developing epilepsy?
  - o What factors contribute to increased risk for epilepsy in the elderly?

- What are other as yet unknown causes and risk factors of epilepsy?
- Mechanisms of epileptogenesis
  - Which candidate mechanisms identified so far are causally involved in epileptogenesis in different forms of epilepsy?
  - What additional mechanisms are involved in epileptogenesis?
- Preventing epileptogenesis
  - How can inflammatory, immune/infectious, or metabolic processes be targeted to prevent epilepsy?
  - Given the diversity across different forms of epilepsy, how can we differentiate between mechanisms at play in any individual or group, and identify which to target for the prevention of epilepsy?
  - What biomarkers will aid in identifying, predicting, and monitoring epileptogenesis, including markers at the time of injury/insult that identify those at risk for epilepsy?
- Does epilepsy progress once established?
- What can the mechanisms and clinical course of epilepsy in rare/less common syndromes tell us about causes and epileptogenesis more generally? For example: Nodding Syndrome (environmental triggers), TSC (epileptogenesis), hypothalamic hamartomas (epileptogenesis), Sturge-Weber syndrome (cerebrovascular/blood-brain barrier related mechanisms), Rett syndrome (genetic interactions contributing to epilepsy risk)
- How can other medical disciplines help to advance epilepsy research and lead to better understanding of disease mechanisms and to improvements in diagnosis, treatment, and prevention? (e.g., expertise in virology, immunology, cerebrovascular system, traumatic brain injury, etc.)

### **Research resources and challenges**

- Animal models for studying epileptogenesis
  - Models of human epilepsies that are well-defined clinically or etiologically
  - Models of epilepsy in aged animals
  - Continued need for clinical and basic researchers to work together to develop models that accurately mimic human epilepsies, and to determine when data are strong enough to move treatment development forward
  - Need for longterm monitoring of large numbers of animals presents practical challenge
- New research technologies and data analysis methods
  - Continued need for sophisticated analytical methods for data produced by next-generation sequencing technologies
  - Application and development of research technologies for imaging, recording, and manipulating neural circuit activity further understanding of mechanisms that predispose, drive, or prevent seizure activity (optogenetics, multielectrode arrays)
  - Application and development of novel clinical/diagnostic technologies to the study of epileptogenesis and biomarker identification (reliable ambulatory EEG, improved EEG algorithms, high frequency EEG components, internet-based patient tracking in real time)
- Challenges in clinical research
  - Few well-defined cohorts of people at risk for developing exists for identifying potential epileptogenesis biomarkers and testing interventions for prevention
  - Need for long term monitoring of large numbers of at risk individuals presents practical challenge
  - 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 progress
  - Phenotyping: how do we tell the different forms of epilepsy apart? Rather than combining cases with likely different etiologies together in genetic studies, how can we put clinical observations, patient and family history, and other factors together to begin to separate phenotypes and understand genetic influence?

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

### **Goals**

- Define gaps in clinical care and change practice through research to develop innovative treatment and diagnostic strategies and to inform the development of evidence-based guidelines
- Develop novel treatment approaches that target specific forms of epilepsy, including new antiseizure drugs, as well as devices, gene therapy, biologics, feed-back driven delivery methods, new methods for resective surgery

### **Advances**

- New syndrome-specific drugs approved (retigabine/ezogabine for partial epilepsies, rufinamide for Lennox-Gastaut, stiripentol for Dravet's, ACTH for infantile spasms), others on horizon
- Recognition that epilepsy is not a simple imbalance between neuronal excitation/inhibition (identification of other mechanisms, including inflammatory processes, role of glia/adenosine)
- Better understanding of the basis of the ketogenic diet and the relationship between energy metabolism and neuronal excitability
- Evaluation of new stimulation devices; non-invasive transcranial focal electrical stimulation; non-invasive trigeminal nerve stimulation
- Validation of the association between HLA-B\*1502 and carbamazepine-induced Stevens-Johnson syndrome in specific Asian populations
- Development of minimally-invasive MRI-guided laser technology for neurosurgery
- Epilepsy surgery advances include Class I evidence supporting early surgery, prospective study of long term outcomes, improvements in some surgical and presurgical mapping techniques
- New/improved technologies and associated analytical methods for mapping epileptic networks, tracking and predicting seizure generation, and potentially epileptogenesis (optogenetics, multielectrode arrays)
- HFOs as marker of epileptic tissue and use in surgical mapping; potential as marker of epileptogenesis as well
- Structural and functional neuroimaging techniques have increased knowledge of widespread brain networks implicated in seizure generation and propagation (and which likely contribute to cognitive, behavioral, sleep, and other disorders).
- New pharmacologic targets identified
- Advances in identifying mechanisms in specific types of epilepsy
- Some progress in animal models toward gene therapy approaches, and more recently antisense RNA
- Emergence of zebrafish as potential intermediate throughput model for epilepsy therapy development
- Studies to understand challenges and consequences of poor medication adherence (may also relate to comorbidities)

### **However:**

- 25-35% of cases remain refractory, and available therapies have adverse side effects, despite some improvements
- No clear genetic, electrophysiological, or imaging markers of drug response; limited markers for adverse effect risk

### **Research questions and opportunities**

- Understanding seizure activity (ictogenesis, propagation, termination)
  - o What are the mechanisms involved in seizures in specific forms of epilepsy? (neuronal circuits, cellular metabolism, factors related to tumor/dysplasia/lesion)
  - o What are the mechanisms underlying seizure termination, and why do they fail in epilepsy and status epilepticus?
  - o How can we better understand epileptic circuits through the application of new technologies for mapping neural activity?
- Development of targeted treatments based on the underlying causes and mechanisms of different types of epilepsy
  - o What mechanisms are sufficiently well understood for a targeted approach?
  - o How can understanding mechanisms inform decisions about the use of currently available treatments for different forms of epilepsy?
  - o Will anti-inflammatory, antiviral, or other immune-related treatments be effective in some forms of treatment-resistant epilepsy?

- How can we further develop brain stimulation approaches for the treatment of epilepsy? (feedback control, combination approaches to potentiate drug treatment, less invasive approaches)
- How does brain/nerve stimulation alter seizures, and what stimulation protocols are needed to reduce seizure activity in any given seizure type?
- Optimizing existing treatments
  - What are the impacts of treatment non-adherence in people with epilepsy, and how can adherence be improved?
  - What factors unique to certain populations, such as infants and children, the elderly, and women, should be considered in terms of treatment selection and identifying and preventing risks for adverse treatment effects or comorbidities?
  - How can we learn from amassed clinical experience to formulate more rationale and integrated delivery of care and health services for people with epilepsy, including which evaluations are appropriate, decisions about best treatment options, genetic counseling, and consideration of comorbidities?
  - Surgery:
    - What accounts for the relatively low use of epilepsy surgery in the United States?
    - How can we improve the effectiveness of epilepsy surgery? (improve selection, referral guidelines, surgical methodologies, etc.)
    - How can surgical outcomes be improved for extratemporal non-lesional epilepsy? (Advances in surgical mapping and outcomes have focused on temporal lobe epilepsy.)
  - Comparative effectiveness research:
    - How do available treatment options compare in terms of efficacy and effectiveness for different types of epilepsy?
    - What delivery methods are most effective for treating acute seizures and status epilepticus?
    - Will polytherapies be more effective than monotherapies in some forms of acute seizures and epilepsy?
- Improving diagnosis, monitoring, and seizure classification
  - How can we better diagnose and classify the epilepsies and different types of seizure activity?
  - How can we better diagnose and classify epilepsy in the developing, aging, diseased, or injured brain? (For example, symptoms of seizures or epilepsy in the elderly such as forgetfulness may be incorrectly attributed to a normal aging process.)
  - How can diagnostic improvements inform treatment selection and monitoring?
  - How can we improve methods for diagnosing and monitoring of epilepsy? (reliable ambulatory EEG, improved EEG algorithms/characterization, high frequency EEG components or other reliable diagnostic markers, internet-based patient tracking in real time)
  - What biomarkers will aid in the identification of seizure onset and localization, and in the prediction and monitoring of treatment response and/or adverse effects?
- Cross-cutting: How can rare syndromes (clinically or genetically defined) inform advances in the diagnosis, classification, and treatment of epilepsy more generally?
  - human tissue research, surgical methods, factors contributing to treatment resistance, targeting mechanisms that may be shared across other types of epilepsy, animal models

### **Research resources and challenges**

- Collaboration, common definitions and standards
  - Leverage/continue to incentivize and facilitate data and resource sharing and to develop standards for clinical techniques (surgical mapping, EEG, etc.) used across research sites and groups
  - Continued collaboration across disciplines also important (pharmacology, bioengineering, computer science and informatics) to continue progress in technology and therapy development
  - Collaboration and classification standards will also be important for large-scale efforts to identify biomarkers of likely drug response or adverse effects
  - A framework for standardizing surgical approaches and classifying a wider range of treatment resistant patients across centers to facilitate testing and comparison of approaches and combinations of approaches

- Collaboration essential for rare disease research
- Shared infrastructure (like NeuroNEXT) may also improve recruitment and quality of trials
- Preclinical research needs
  - Animal models for specific forms of epilepsy, for use in developing and testing therapeutic approaches (drugs, biologics, or stimulation) that target specific underlying mechanisms.
  - Preclinical and other criteria for selecting high quality research to move forward in clinical trials
  - Continued progress to develop and apply new technologies for monitoring neural activity (including large-scale/long-term monitoring in animals and noninvasive approaches for monitoring in humans)
- Challenges related to conducting clinical trials
  - Recruitment is difficult, in part due to availability of 17 AEDs
  - Heterogeneity across subjects
  - Variable expertise and experience across trial sites; increasing globalization adds to variability
  - Assessing advances in surgical approaches also limited by need to have patients undergoing surgery in centers with the necessary technical expertise and equipment
  - Absence of biomarkers or early indicators of treatment response
  - Regulatory roadblocks and needs for new trial designs/approaches
  - More incentives, infrastructure, and reduced regulatory barriers are needed to facilitate comparative efficacy research to determine optimal treatments and point-of-care guidance.

## ***Benchmarks Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment.***

### **Goals**

- Understand the range, prevalence, severity, and course of comorbidities beyond seizures in people with epilepsy.
- Understand risk factors and underlying mechanisms of comorbidities, and develop effective approaches to diagnosis, treatment, and prevention.
- Understand risk factors and mechanisms involved in increased mortality in people with epilepsy, including SUDEP and suicidality, and develop effective preventive strategies.
- Understand risk factors and mechanisms involved in non-epileptic seizures (NES), and develop effective approaches for diagnosis and treatment.

### **Advances**

- Increasing recognition of comorbidities and the bidirectional relationships between the underlying causes of epilepsy, seizures, and comorbidities
- Structural and functional neuroimaging techniques have increased knowledge of widespread brain networks implicated in seizure generation and propagation and which likely contribute to cognitive, behavioral, sleep disorders, and other comorbidities
- Development of animal models of cognitive and behavioral comorbidities in acquired and genetic epilepsies in both immature and mature animals, and identification of potential underlying mechanisms and targets for intervention
- Evidence that SSRI treatment is effective for depression in people with epilepsy and does not appear to exacerbate seizures; self-management and CBT programs also show promise for addressing mood disorders and other issues affecting quality of life
- New insights into SUDEP mechanisms and risk factors and efforts to develop preventive interventions, resulting from interdisciplinary collaboration between basic and clinical research (cardiac, autonomic, respiratory)
- Increased understanding of risk factors and treatment options for non-epileptic seizures (NES)
- Growing evidence base to define risks of in utero exposure to antiepileptic drugs, resulting in recommendations for pregnancy counseling and care in women with epilepsy
- Advances in predicting or preventing effects of treatment, such as improvements in presurgical mapping that may help predict risk of decline and early screening to identify adverse AED effects
- Further characterization of sleep disorder subtypes and therapy, particularly obstructive sleep apnea syndrome
- Recognition of relationship between seizure patterns and sleep/wakefulness and sleep-dependence of behavioral comorbidities, and memory and cognitive dysfunction in epilepsy patients
- Studies to understand challenges and consequences of poor medication adherence may also relate to comorbidities

### **However**

- Despite the relatively high prevalence of psychiatric and other comorbidities in epilepsy, limited high-quality, controlled data exist to demonstrate the safety and efficacy of available treatment options.
- Limited study overall of adverse effects of treatments/role of treatment in comorbidities.
- Interventions do not exist to prevent comorbidities or increased mortality (including SUDEP) in people with epilepsy.

### **Research questions and opportunities**

- Characteristics of cognitive, psychiatric, and behavioral comorbidities
  - o How do comorbidities and quality of life in people with epilepsy compare with those in people with general medical illnesses or other neurological disorders? (most existing research/information compares people with epilepsy to healthy controls)
  - o How does cognitive function vary across a population-based cohort of adults with epilepsy?
  - o What are the patterns of neurobehavioral comorbidities across different types of epilepsy? Which comorbidities are shared, and which are specific to certain syndromes?
  - o What is the natural history of structural and cognitive outcomes from the time of epilepsy diagnosis, and what are the contributions of ongoing seizures and epilepsy treatments?
- Contributing factors and underlying mechanisms of cognitive, psychiatric, and behavioral comorbidities
  - o What are the causes and mechanisms of mental health comorbidities in different forms of epilepsy?

- How do seizures and/or the underlying cause of seizures affect the developing brain, and can effects, such as intellectual disability, be prevented or reversed? How will intervention impact the developing brain, and what are the implications of ongoing development for therapeutic options and the timing of treatment?
- What are the mechanisms underlying psychological or other comorbidities in rare syndromic epilepsies, and how can they provide insights into the comorbidities of epilepsy more generally? (e.g., neuropsychological and endocrinological impacts of hypothalamic hamartoma)
- How is treatment non-adherence related to comorbidities and quality of life in people with epilepsy?
- Risk factors, biomarkers, and screening for comorbidities
  - What molecular, neuroanatomic, or other biomarkers and diagnostic screening approaches might identify individuals at risk for comorbidities, or aid in monitoring outcomes? How can research findings on markers and diagnostic screening programs for comorbidities be translated into clinical practice?
  - What are risk factors for suicide in individuals with epilepsy and psychiatric comorbidities?
  - How can cognitive and behavioral adverse effects of treatment (medication, surgical, or other) be predicted or identified early, in order to allow intervention?
- Treating and preventing cognitive, psychiatric, and behavioral comorbidities
  - What behavioral treatments will be effective for persons with epilepsy and mental health comorbidities? (including interventions to be used along with medical approaches and programs that focus on treatment adherence, self-management, and/or quality of life)
  - How can knowledge about risk factors, mechanisms, and natural history of comorbidities be translated into the development of preventive strategies?
  - How can exacerbation of cognitive comorbidities by epilepsy treatment be avoided?
  - Are treatments for psychiatric comorbidities in the general population safe and effective in people with epilepsy? (consensus statements developed recently are based largely on expert experience, given limited high-quality data from controlled clinical trials)
- Psychosocial impact of epilepsy diagnosis
  - What are the psychological and social impacts of an epilepsy diagnosis on patients and their families?
  - Would counseling help newly diagnosed patients understand what to expect and how to manage their health?
  - What interventions will address the psychosocial needs of children with epilepsy and their families, including needs related to adjustment, coping, depression, and anxiety in youth who develop comorbidities?
- SUDEP
  - What are risk factors for SUDEP? What genetic or other markers might identify individuals at risk?
  - How can SUDEP be prevented in those at risk?
  - How can research findings on molecular predictors, biomarkers, and diagnostic screening approaches for SUDEP be translated into clinical practice?
- Sleep and epilepsy
  - What sleep disorders occur in people with epilepsy?
  - How are aspects of sleep, including circadian periodicity and sleep patterns/structure, related to epilepsy and seizure occurrence? How can understanding these interactions inform diagnosis and treatment?
- Other comorbidities of epilepsy or consequences of epilepsy treatment
  - What are the effects of all available antiepileptic drugs on the anatomic and neuropsychological outcomes of children exposed to these agents *in utero*? What other pregnancy outcomes are associated with antiepileptic drug use? (e.g., rates of caesarian sections and rates of low birth weight)
  - Are rates of infertility and other endocrine disturbances increased in people with epilepsy, and (if so) what are the underlying mechanisms?
  - Why are people with epilepsy at increased risk of bone health problems? What screening approaches will identify bone health problems and what are options for treatment?

- Non-epileptic seizures (NES)
  - What are risk factors and underlying causes of NES? Would a prospective trial following patients with risk factors previously identified retrospectively (trauma, developmental privation) better establish susceptibility factors and etiologies?
  - How are NES related to mild traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD)?
  - What treatments will be effective for NES?

### **Research resources and challenges**

- Characterizing comorbidities of epilepsy and determining causes and risk factors
  - More interdisciplinary or cross-disciplinary research teams and collaborations are needed, including prospective, multicenter studies
  - A substantial proportion of the literature on comorbidities in epilepsy is based on analyses of administrative data sets, which are limited for providing more than trends (i.e., lack details related to severity of comorbid conditions)
- Animal models:
  - The development, utility and applicability of animal models of comorbidities would be facilitated by a more precise characterization of the human condition
  - Measurable and reliable outcomes that resemble the human condition need to be developed
  - Need improved technology for *in vivo* monitoring of potential biomarkers for comorbidity prediction, progression, and treatment response
  - New analytical platforms needed for the discovery of new candidate genes for comorbidities
- SUDEP:
  - Suspected risk factors and pathophysiologic mechanisms are difficult to prove because of the unpredictable occurrence of SUDEP, which is mostly in the community setting distant from investigating centers, and because of the low rate of complete autopsies
  - Opportunities exist in focusing on large prospective cohorts of high-risk patients for validating preventative strategies
- NES:
  - There is no diagnostic test for NES that is cost-effective, operator-independent, and that can be performed in an outpatient setting. NES diagnosis is based on long-term video EEG (VEEG) monitoring, which is expensive and restricted to specialized epilepsy centers. Identifying NES in patients with epilepsy requires several days of inpatient VEEG monitoring.