Epilepsy Benchmarks Area IV: Limit or Prevent Adverse Consequence of Seizures and Their Treatment Across the Life Span

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Abstract

Epilepsy represents a complex spectrum disorder, with patients sharing seizures as a common symptom and manifesting a broad array of additional clinical phenotypes. To understand this disorder and treat individuals who live with epilepsy, it is important not only to identify pathogenic mechanisms underlying epilepsy but also to understand their relationships with other health-related factors. Benchmarks Area IV focuses on the impact of seizures and their treatment on quality of life, development, cognitive function, and other aspects and comorbidities that often affect individuals with epilepsy. Included in this review is a discussion on sudden unexpected death in epilepsy and other causes of mortality, a major area of research focus with still many unanswered questions. We also draw attention to special populations, such as individuals with nonepileptic seizures and pregnant women and their offspring. In this study, we review the progress made in these areas since the 2016 review of the Benchmarks Area IV and discuss challenges and opportunities for future study.

Keywords

NINDS benchmarks for epilepsy research, epilepsy benchmarks, comorbidities, cognition, psychogenic nonepileptic events, PNES, mortality, sudden unexpected death in epilepsy, pregnancy, consequences of treatment
Introductory Vignette: A Parent’s Perspective by Monika Jones

In 2007, our 2-week-old son Henry was referred for an epilepsy surgery consultation regarding candidacy for hemispherectomy for frequent and clustering seizures caused by total hemim céphalencephaly. A brain MRI revealed a unilateral malformation and all seizures originated from the left side of the brain. Henry needed to gain weight prior to hemispherectomy surgery, and in the intervening months, he was given a cocktail of 4 anti-seizure medications and then a fifth when infantile spasms began. At that time, he had made no developmental progress since infancy. At almost 4 months old and of sufficient weight, a modified lateral hemispherotomy was performed. Seizures stopped for 9 months and he showed a positive developmental trajectory, including bottle feeding, arm crawling, and babbling. Seizures returned but were controlled with topiramate. At 18 months old, and almost 1.5 years after hemispherotomy, Henry developed hydrocephalus and received a ventriculoperitoneal shunt. At that time, our son had developed approximately 20 words and was bearing weight on his legs. Seizures once again became uncontrolled and a reoperation was performed to sever missed white matter connections. Seizures returned almost immediately, and he was once again placed on a cocktail of antiepileptic drugs. During this time, Henry lost all spoken words and developed severe features of autism but learned to walk. A total hemispherectomy was performed the following year. While our son’s developmental progress improved, spoken words never returned. Five shunt revisions have been required for chronic hydrocephalus and an internal cranial vault expansion was performed but collapsed, requiring reconstruction. Our son has since developed endocrine and vision impairments, and abducens nerve palsy as a result of chronic hydrocephalus and has required multiple orthopedic surgeries to correct other consequences of surgically induced hemiparesis. In no other disease space would removing half a child’s brain be an acceptable cure, but for some reason, we accept this for epilepsy. Our story illustrates the importance of understanding and improving approaches for epilepsy surgery, potential comorbidities, as well as the functional implications of large epilepsy surgeries.

Monika Jones of Brain Recovery Project

Introduction to comorbidities

Benchmarks Area IV focuses on comorbidities that often impact individuals with epilepsy and their families, including the impact of seizures and their treatment on quality of life, development and cognitive function. In this section, common medical conditions, psychiatric issues, and biomarkers of cognitive changes are reviewed.

Common Medical Comorbidities

Epidemiological studies have demonstrated that individuals with epilepsy are at high risk for medical comorbidities. In a Scottish population-based, cross-sectional study of individuals older than 14 years, it was reported that 69.9% of individuals with epilepsy had 1 or more comorbid health conditions, and almost 1 (18.6%) in 5 presented with 4 or more conditions, compared to 46.9% and 9.0% in people without epilepsy from a national health service data registry over 1 million youth and adults. A retrospective, population-based study assessed the prevalence and predictors of medical comorbidity to hypothesize mechanisms underlying the comorbidity burden in persons with epilepsy seen at a tertiary care center and in the community across regions of the United Kingdom. The presence of a structural cause of epilepsy was associated with a lower odds ratio for comorbidities. A shorter epilepsy duration was also associated with a lower risk of comorbidities, indicating that, at the time of epilepsy diagnosis, there is a high proportion of medical comorbidity burden. Among the tertiary care cohort, female sex represented a risk factor for endocrine, metabolic, nutritional, and musculoskeletal comorbidities.

Psychiatric and Neurological Comorbidity

The epilepsy literature has reflected long-standing recognition of the association between chronic seizures and cognitive and mental health disorders. An evolving concept is that seizures may be one symptom of broader neurological pathologies that also cause cognitive and psychiatric symptoms, as discussed in the review for Benchmarks Area I. With expanding use of next-generation sequencing in research studies and clinical care, there are increasingly recognized shared genetic causes of developmental and epileptic encephalopathy, autism spectrum disorder, intellectual disability, and schizophrenia. One gene associated with a number of these conditions, at times even in the same patient, is SCN2A. De novo variants in overlapping candidate genes targeting cortical development, synaptic transmission, and ion transport were found in probands at higher prevalence rates compared to controls.

Early studies in individuals with epilepsy have identified an association between impaired memory performance and single-nucleotide polymorphisms (SNPs) in genes encoding proteins with known synaptic functions, revealing similarities with neurodegenerative cognitive disorders such as Alzheimer disease and normal aging. The specific mechanisms through which these SNPs might modulate the function of the related genes warrant further study. For patients with complicated presentations including intellectual disability and psychopathology, utilizing a “genomic-first” approach to identify etiology may be increasingly appropriate. Well-powered studies are needed to perform genome-wide analyses that appropriately account for multiple testing.

Emerging Clinical Biomarkers of Cognitive Comorbidities

Identification of biomarkers that predict or reflect epilepsy comorbidities remains an important focus to inform classification, prognosis, and treatment development. Imaging is a clinically accessible means to gain insight into brain-based...
mechanisms of cognitive comorbidities. In a study of adults with temporal lobe epilepsy (TLE), impaired performance IQ and visuospatial memory were associated with reduced structural brainstem connectivity, while impaired verbal IQ and language function were related to diminished functional connectivity. In one study of patients with juvenile myoclonic epilepsy, cognitive performance was positively correlated with N-acetyl aspartate to creatine ratios in bilateral frontal and thalamic regions, as measured by magnetic resonance spectroscopy. These imaging studies indicate that networks outside the epileptogenic zone may be impacted or play a role in pathogenesis, which will be important in the development of novel therapeutic targets. Further work is needed to both explore and validate these and other such biomarkers.

The utility of neuroimaging biomarkers has been demonstrated in children with tuberous sclerosis complex (TSC) in 2 studies. Diffusion tensor tractography studies examining corpus callosum integrity found lower fractional anisotropy in patients with TSC compared to control children and compared to control children with nonsyndromic autism. The magnitude of callosal white matter changes correlated with increasing number of comorbid conditions. In the second study, the degree of cerebellar volume differences correlated strongly with the severity of neurodevelopmental impairment, particularly for TSC2 variants. Increasingly genetic and imaging results may converge to further delineate molecular mechanisms from model-based research, defining timing and age-specific vulnerabilities that lead to comorbidities associated with epilepsy.

Consequences of Antiseizure Treatments

The comorbidities common to individuals with epilepsy may, in some cases, be directly influenced or even caused by the treatments given for seizures.

Antiseizure Medications

Since 2016, 2 third-generation antiseizure medications (ASMs) were approved by the Food and Drug Administration: cannabidiol (CBD) and brivaracetam. In a multicenter retrospective study of children with intractable epilepsy using an oral formulation of CBD, improvement was noted in behavior and alertness, language, communication, motor skills, and sleep as measured by the adverse events profile. However, for individuals with Dravet syndrome, treatment with CBD was not found to significantly impact quality of life or adaptive function in a double-blind, placebo-controlled trial. Note that these measures were not the primary study outcomes. Retrospective studies of brivaracetam showed a range of psychiatric adverse events, including depression, suicidal ideation, irritability, aggression, and psychosis.

For ASMs that have been in clinical use prior to 2016, a retrospective comparative effectiveness study of patient records reported that psychiatric and behavioral side effects occurred more often among individuals taking levetiracetam and zonisamide, leading to high rates of intolerability.

The very terminology that we use in the field, including the relatively newly agreed-upon term “antiseizure medication,” underscores the focus on seizure control, which is inherently important and often the most pressing issue for patients presenting with new-onset epilepsy or with seizure exacerbations. However, long-standing clinical observation adds to accruing evidence that epilepsy is but one symptom of a multisystem neurodevelopmental disorder, increasingly with a single unifying cause identified. For parents of children with severe epilepsies, the nonseizure symptoms may be as pressing or more urgent than the seizures themselves, and drug trials will need to account not only for biomarkers but also for health-related quality-of-life measures.

Dietary Therapy

Most published reports on ketogenic dietary therapies use seizure-related outcomes as the only reported end point. However, there have been several published studies since 2016 which address cognitive comorbidities, compiled in a review by van Berkel et al. Both the classic ketogenic diet and the modified Atkins diet are suggested to improve cognition and other developmental domains in children with epilepsy, although studies thus far have been small and show differing effect sizes.

Epilepsy Surgery and Neurostimulation

In addition to more traditional surgical procedures, several novel surgical approaches to the treatment of drug-resistant focal epilepsy were developed in recent years, including laser interstitial thermal therapy (LITT) and neuromodulation of the anterior nucleus of the thalamus with deep brain stimulation (DBS) as well as responsive neurostimulation (RNS). Recent publications on LITT reported preliminary results suggesting that this therapy was associated with better cognitive outcome than open resections in many circumstances. Among individuals with drug-resistant mesial TLE who were treated with a brain-responsive neurostimulator, Geller et al reported serious adverse events, including depression and suicidality. In individuals with epilepsy treated with DBS of the anterior nucleus of the thalamus, there was no worsening of depression or cognitive scores. Seven years after treatment, there were improved scores on tests of executive function and attention. As newer approaches are integrated into clinical care, systematic and standardized evaluations of comorbidity outcomes in the short and long term will be important to evaluate and compare treatment effectiveness.

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures (PNEEs), thought to be a physiological response to psychiatric distress, require high rates of medical resources associated with elevated medical
costs, including emergency department resources as well as inpatient epilepsy monitoring unit visits. Practice guidelines for the diagnosis of PNES were developed in 2013, and more recent focus has been on treatment gaps across cultures with the International League Against Epilepsy NES Task Force report. A recent study sought to provide information on prevalence, risk factors, and psychiatric comorbidity in these varied groups. Outside the United States and European countries, access to diagnostic tools, standardized methods for assessment, and communicating the diagnosis remain challenging. A multicenter study found a clear relationship between diagnostic and treatment services for PNES and a country’s economic status.

When standardized diagnostic procedures and a uniform approach to initial treatment of symptoms were utilized, a positive impact on quality of life was reported. Treatment was the largest area of growth in research on PNES; however, few studies were randomized controlled trials. Specific types of treatment were explored, such as prolonged exposure therapy (evidence-based cognitive–behavioral therapy, CBT) in individuals with PNES and posttraumatic stress disorder and abbreviated CBT-based psychoeducation. A meta-analysis of 13 eligible treatment studies included CBT and other modalities with reported improvement for individuals engaging in treatment as opposed to those who did not attend treatment for PNES. Similarly, a prospective follow-up study of adults with PNES was found to have decreased emergency room utilization and improved quality of life in association with adherence with psychotherapy.

There continues to be a lack of providers engaging in treatment for PNES. Based on limited data, long-term outcomes appear to be poor, particularly in the absence of treatment. Finally, given known unique risk factors in children, future treatment trials should include diverse populations, including those with concurrent epilepsy using an interdisciplinary approach.

**Mortality—Mechanisms, Potential Targets for Treatment**

Epilepsy-related mortality poses a serious public health burden and is second only to stroke in terms of years of potential lives lost to neurological disease. In 2017, the International League Against Epilepsy (ILAE) Mortality Task Force reported that the major causes of mortality for individuals with epilepsy include status epilepticus, SUDEP, and injuries. Standardized mortality ratios were slightly higher in males, individuals less than 45 years, and groups with static or progressive encephalopathies were at high risk for mortality. In 2017, the American Academy of Neurology and the American Epilepsy Society published practice guidelines for SUDEP. Based on meta-analysis of 12 studies, the overall risk for SUDEP is 0.58 per 1000 patient-years, while the risk is 0.22 and 1.2 per 1000 patient-years in children and adults, respectively. For particular subgroups such as Dravet syndrome, the SUDEP rate was estimated as 9.32 per 1000 person-years.

Substantial investment by National Institute of Neurological Disorders and Stroke (NINDS) and other nonfederal initiatives have accelerated progress in SUDEP research. In late 2014, NINDS funded the Center for SUDEP Research, a 5-year Center Without Walls including 14 collaborating institutions. Goals included both basic science and clinical research, contributing over 30 publications. Since 2016, there has also been significant ongoing investment by nonprofit foundations focused on understanding basic mechanisms and biomarker discovery as well as national registries that gather clinical information and DNA for cases of sudden and unexpected death, including SUDEP.

In clinical studies, functional magnetic resonance imaging has been used to show alterations in functional connectivity between key autonomic regulatory regions in TLE with high SUDEP risk, and alterations in cortical thickness in key cardiovascular, respiratory, and somatosensory regions in individuals with generalized tonic–clonic seizures relative to healthy individuals. Studies have also suggested that postconvulsive central apnea and low interictal hypercapnic ventilatory response may serve as potential clinical biomarkers for SUDEP risk.

Studies in animal models of SUDEP continue to advance our understanding of underlying mechanisms. Recent advances include the ability to simultaneously record electrocardiogram, electroencephalogram, and respiration in mice, which can provide clues about sequencing of events. Respiratory dysfunction was evident in Kcna1-null mice, Scn1a mice, and the DBA/1 SUDEP model. Several studies have implicated brainstem cardiorespiratory centers as critical mediators of SUDEP and suggested that serotonin neurons are major contributors. Other studies hypothesized intrinsic cardiac arrhythmia phenotypes as another SUDEP mechanism. Relevant to Dravet syndrome and SCN1A, cardiomyocytes differentiated from patient-derived induced pluripotent stem cells (iPSCs) have abnormal physiology, suggesting cardiac arrhythmias may contribute to SUDEP. The epileptic encephalopathy-associated Scn8aN1768D mouse model has a cardiac arrhythmia phenotype evident in isolated cardiomyocytes, supporting contribution of a cardiac mechanism in addition to central nervous system dysfunction. Acquired cardiac arrhythmias may be a consequence of epilepsy. In one study in a kainic acid-induced epilepsy rat model, the induction of epilepsy led to longer ventricular action potential durations due to elevated expression of tetrodotoxin-sensitive neuronal sodium channels in the heart. Similar to human studies, it appears that background genome variation can shape SUDEP risk, with several studies demonstrating that varying combinations of risk and protective alleles in modifier genes can influence SUDEP susceptibility.

The US National Violent Death Reporting System estimated annual suicide rate in persons with epilepsy was 22% higher than the general population. A United Kingdom population-based study found 2.9-fold increased risk for suicide attempt prior to epilepsy diagnosis, suggesting common underlying etiology. Medication use can also contribute, particularly...
medications taken for comorbidities common to patients with epilepsy. For example, a United Kingdom population-based study reporting a 5-fold risk for unintentional medication poisoning and a 3.55-fold risk for intentional medication poisoning, with opioids and psychotropic medications being the most common medications. However, a discussion on medication use and mortality should also emphasize that one of the risk factors for SUDEP is a history of nonadherence to treatments.

Sustained momentum will help address remaining challenges, including continued development of reliable SUDEP biomarkers and preventative measures, as well as continued natural history and epidemiological studies to advance clinical trial readiness. In addition, continued basic science research on underlying mechanisms of SUDEP will support translational studies in humans, including development of biomarkers and testing of interventions. Attention and funding for other treatable causes of epilepsy-related mortality (eg, psychiatric comorbidity) has lagged relative to SUDEP and remains an unmet need.

Special Populations in Epilepsy

The clinical care of women with epilepsy of childbearing potential should incorporate several important factors, including prevention of unintended pregnancies, preconception planning, and understanding of the benefits and risks of ASMs taken during pregnancy on the mother and fetus.

In women seeking pregnancy, one recent study reported no differences in pregnancy rates, time to pregnancy, and live birth rates in women with epilepsy versus women without epilepsy. Enzyme-inducing ASMs may lower the efficacy of hormonal contraception, as reported by an increased rate of unintended pregnancy in a retrospective study from the Epilepsy Birth Control Registry (EBCR). The EBCR also showed that only 69.7% of women “at risk” of becoming pregnant used highly effective contraception, and only 25.4% consulted with their neurologist regarding contraceptive methods. Conversely, another study showed that only 37% of women with epilepsy were counseled by their neurologist about contraception.

Data continue to accrue, showing that valproate use during pregnancy has many potential negative consequences on the developing fetus, including higher rates of major congenital malformations (MCMs) and reduced cognitive abilities in the child, a concern that has been highlighted to the clinical community with a position statement by the American Epilepsy Society. Data on the newer ASMs also continue to accumulate and, thus far, levetiracetam and lamotrigine appear to be generally safe. The rates of MCM are higher with polytherapy, especially when topiramate or valproate was involved. Some drugs, such as topiramate, have been reported to have higher rates of MCM at the higher doses typically used for epilepsy compared to lower doses for other conditions. Regardless of maternal use of ASMs, there were overall higher rates of prematurity and lower birth weights in infants born to women with epilepsy.

Epilepsy pregnancy registries worldwide have recently published updated data comparing current versus prior ASM prescribing patterns. Antiseizure medication monotherapy was more common using lamotrigine and levetiracetam, and polytherapy most commonly involved these in combination. With increasing awareness of teratogenic effects, overall use of polytherapy and any regimen with valproate was reduced compared to the past. For example, in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study, only 4 (1.1%) of 351 women were on valproate. The Taiwanese Registry of Epilepsy and Pregnancy showed that in 2004, 73.3% of women were on “first-generation” drugs (ie, drugs developed before 1993, including drugs like valproate, phenobarbital, and carbamazepine), but only 8.3% were on those drugs in 2015. Similarly, in 2004, 40% of women were on polytherapy compared to 20% in 2015.

Folic acid is a primary pharmacologic intervention to help reduce the rate of MCMs, particularly in light of unintended pregnancy. However, the EBCR showed that less than half of women with epilepsy “at risk” of becoming pregnant took folic acid supplements. In addition to folic acid helping to prevent neural tube defects, studies showed that children exposed to ASMs in utero had a lower risk of autistic traits and language delay if the mother used periconceptional folic acid supplements.

Ongoing studies of teratogenicity in the newer ASMs, polytherapy combinations, and other treatment modalities (eg, ketogenic diet, vagus nerve stimulation, RNS) are critically needed. There is also a need to improve methods of communicating information to women about therapeutic and prevention measures for reducing maternal and fetal risk during pregnancy without compromising treatment for epilepsy.

Future Directions: Challenges and Opportunities

Despite awareness of the significance of the comorbidities and consequences of the epilepsies, there remain gaps in knowledge and ongoing challenges to implement research findings into clinical practice.

Multicenter longitudinal studies are needed for new-onset epilepsy using standardized assessments and patient-centered methods that will help define the natural history of epilepsy comorbidities. For more complex genetically based epilepsies, discovery and validation of clinical biomarkers using larger well-characterized groups and common data elements will be needed. Advances in technology are allowing the generation of new disease models that carry patient-specific mutations, for example, in vitro models generated with CRISPR or other techniques in conjunction with patient-derived iPSCs. In parallel with the use of animal models, these advances will likely shed new light on underlying mechanisms and potential therapies. Given multiple neurobiological effects of epilepsy-relevant genes on brain networks, more studies need to be done to differentiate gene effects on epilepsy prognosis, brain development, and associated comorbidities. These studies will help...
identify critical windows during development and delineate strategies for the identification of novel therapeutic targets and the development of new treatments.

Although genomic approaches continue to identify pathogenic mechanisms, it is also critical to simultaneously advance our recognition of cognitive and psychiatrically based phenotypes in epilepsy. Standardization and characterization of phenotypes could lead to identification of candidate circuitry. Through neuroimaging and data modeling, application of what is already known about network disruptions in depression and cognitive decline may complement what is known about genetically based epilepsies and may lead to a more integrated model of the bidirectional nature of comorbidities and the epilepsies. Focusing on the comorbidities as part of an epilepsy phenotype could shift classification and inform pathogenic mechanisms and treatments.

The prioritization of Benchmarks Area IV has contributed to major advances, for example, as seen in preclinical research on multimodal methods for the prevention of SUDEP. It will be important to continue efforts to reduce epilepsy mortality as well as to advance progress on other benchmarks. Progress will be greatly aided by identification of candidate biomarkers of the comorbidities of epilepsy using genomic, imaging, and clinical measures in animal and human studies. Given the increasing inter-relatedness of psychiatric disorders and epilepsy, the need has never been greater to assemble teams of specialists in neurology, psychiatry, psychology, neuropsychology, and other fields to advance research and develop therapies for epilepsy across the life span while considering special populations, improving quality of life, and reducing mortality.

Ultimately, addressing the comorbidities in the context of treatment studies will be necessary to obtain the quality data needed to advance personalized care using a research-informed and interdisciplinary approach. Currently, treatment studies underreport comorbidity outcome data. When the data are reported, a lack of standardization hinders the ability to compare across studies. Looking toward the future, the standardized use of nonseizure outcome metrics, such as the National Institutes of Health Toolbox, Neuro-QoL, and PROMIS measures, could be strongly suggested for grants and publications.

In conclusion, epilepsy is a complex disorder that often features psychiatric comorbidities before, during, and after active disease, which impacts morbidity and mortality, quality of life, and with significant impact on the health-care system. Increased consideration of the comorbidities as an “essential” component of epilepsy can reframe scientific inquiry, therapeutic approaches, and outcomes research considering patients as a whole.

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