Partners Against Mortality in Epilepsy Conference Summary

**Moderator Summaries**
Jeffrey Buchhalter MD, PhD, Gardiner Lapham RN, MPH

The second Partners Against Mortality in Epilepsy conference occurred in Minneapolis, MN, from June 19–22, 2014. This conference, as well as the one in 2012 (1), grew out of the desire to provide a forum in which the most recent information regarding mortality in epilepsy, especially Sudden Unexpected Death in Epilepsy (SUDEP), could be shared by all stakeholders: the bereaved, people living with epilepsy, families, basic scientists, clinical scientists, and advocacy and research organizations. To this end, the conference was built around plenary sessions so that all could and would attend presentations that were designed to be accessible to multiple levels of scientific and clinical backgrounds. The speakers did an outstanding job in this regard. The topics were expanded from the 2012 conference focus on SUDEP to include: other important causes of mortality in epilepsy (e.g., suicide, accidents), the process of grief related to epilepsy, upcoming epilepsy mortality surveillance efforts and provider guidelines. Potential mechanisms underlying SUDEP (genetic, respiratory, cardiac, and autonomic) were discussed in detail by some of the most prominent scientists in the field. In addition to the more didactic plenary sessions, attendees were provided the opportunity to participate in smaller discussion groups intended to provide a more in-depth review of scientific topics for those interested.

As for the first meeting, this conference was accomplished by the hard work of volunteers of our “partner” organizations, including the American Epilepsy Society, Epilepsy Foundation, Citizens United for Research in Epilepsy, Finding a Cure for Epilepsy and Seizures, Danny Did Foundation, and the National Institute of Neurological Disorders and Stroke. The essential contributions of Ms. Cyndi Wright (SUDEP Institute/Epilepsy Foundation) and Mr. Jeffrey Melin (American Epilepsy Society) must be gratefully acknowledged. Similarly, thanks go to all the speakers and moderators who so graciously gave their time and knowledge to make this such a successful and meaningful meeting. A complete list of the generous sponsors and slides presented at the conference are available online (2).

**References**

**Summary Session: Overview of Mortality in Epilepsy Including SUDEP**
Moderator: David J. Thurman, MD, MPH

**Overview of Short- and Long-Term Mortality in Epilepsy**
On average, the overall risk of premature mortality among people with epilepsy, measured by the standardized mortality ratio (SMR), appears to be 2–3 times higher than that of the general population. This risk varies greatly among subgroups with epilepsy, depending on several factors such as the cause of epilepsy. In defining “epilepsy-related” deaths, it is important to separate those attributable directly to epilepsy or seizures from those attributable to underlying neurologic diseases causing epilepsy.

Deaths attributable directly to epilepsy include sudden unexpected death in epilepsy (SUDEP) as well as some cases of fatal status epilepticus. The true incidence of epilepsy-caused mortality is unknown, as national mortality records provide inaccurate data on epilepsy. Therefore, estimates must rely on extrapolations from studies of limited populations, population- or clinic-based, with substantial potential for error. Combined data from a few prospective population-based studies conducted by medical examiners yield an estimated annual rate of SUDEP of 1.22 cases per 1,000 people with epilepsy, a rate corresponding to nearly 2,800 deaths from SUDEP in the United States each year (1). SUDEP incidence varies by age: much lower among young children, higher among adoles-
Deaths attributable to underlying diseases causing epilepsy include those resulting from brain tumors, cerebrovascular disease, central nervous system infections, as well as some inherited disorders. Among people with epilepsy due to these causes, the risk of premature mortality is much higher, particularly in the first few years following diagnosis. Cohort studies of patients newly diagnosed with epilepsy yield variable estimates but consistently show highest risks in the first year following diagnosis and with a median reported SMR of 7 (2). Among all people with epilepsy, the majority of deaths in the first two years after diagnosis appear due to these underlying causes. It follows that among people newly diagnosed with idiopathic epilepsy, an early mortality risk elevation is not observed (2). It should also be noted that age is an important determinant of the risk of premature mortality in people with epilepsy. Younger age is associated with higher SMRs in studies both from higher income as well as developing countries (3). Among older adults, SMRs for those with epilepsy show only modest elevation compared to general populations, a finding attributable in large measure to the increased rates of mortality in general populations of seniors. Although there is consistent evidence that premature mortality in epilepsy is driven substantially by the underlying causes of epilepsy, this phenomenon still requires further study.

Occurrence and Risk Factors for Accidents in Epilepsy
Presented by W. Allen Hauser, MD

Accidental injury due to seizures is an important consideration among the causes of increased mortality in people with epilepsy (3, 4). Several studies point to an increased occurrence of accidental injuries in this population. Most such injuries are relatively minor, but among more serious injuries are fractures, traumatic brain injury, near-drowning or drowning, and burns. Significant increase in the risk of mortality due to accidents have been found in studies of people with epilepsy in the United States, Sweden, and Iceland, with SMRs ranging from 2.4 to 5.6. Some other studies, however, have yielded smaller, statistically insignificant measures of increased risk. Relatively few studies have adequately evaluated specific causes of accidental death among people with epilepsy. There are insufficient data with respect to traffic injuries, where it is important to distinguish among injured persons who were drivers, passengers, or pedestrians. In contrast, several studies have shown a disproportionately high frequency of drowning deaths among people with epilepsy, as found in Alberta, Canada; Great Britain; and King County, United States. In studies in China, Bangladesh, and Taiwan, SMRs for drowning among people with epilepsy ranged from 9 to 40. Burns are frequent accidents in people with epilepsy, but these seldom lead to death in developed countries. In low-income countries, however, burns account for a substantial proportion of deaths in people with epilepsy, with reports of 5% in Tanzania and 20% in Bangladesh. Finally, people with epilepsy are generally recognized as having an increased risk of traumatic brain injury as a result of falls, commonly as a consequence of seizures. There is, however, scant information describing the magnitude of this risk.

References
Summary of Session: SUDEP Mechanisms: Respiratory

Moderators: George B. Richerson MD, PhD, Lisa M. Bateman, MD, FRCPC

The goal of this session was to discuss research on how seizures interfere with neural control of breathing in humans and in animals. Parallels between SUDEP and sudden infant death syndrome (SIDS) were described since there appears to be overlap between the mechanisms involved in seizure-induced respiratory arrest and those that cause apnea during sleep in infants. This was followed by data that provide insight into potential cellular, molecular, and genetic defects that may increase the risk of SUDEP, including evidence for links to serotonin, adenosine, and some long QT gene mutations, each of which may increase the chance for unstable respiratory rhythm generation. These data may lead to a better understanding of why seizures are frequently associated with respiratory dysfunction and to development of novel strategies to reduce the risk of SUDEP.

Human Peri-ictal Physiology: Respiratory

Presented by Lisa M. Bateman, MD, FRCPC

Some form of respiratory distress is frequently reported in witnessed cases of SUDEP and near-SUDEP. While the respiratory rhythm is generated by brainstem neurons, it can be influenced by multiple cortical areas, including those frequently involved in seizures. This talk focused on studies of peri-ictal respiratory function in human seizure recordings obtained in epilepsy monitoring units. Ictal apneas, about 2/3 of which are central, more commonly occur in seizures with electrographic evidence of bi-hemispheric involvement (1). Several studies have demonstrated the frequent occurrence of ictal hypoxemia, though the clinical characteristics correlated with this finding vary (2–4). Peri-ictal hypoxemia is seen in about 1/3 of focal onset seizures, with a delay of approximately 1 minute after seizure onset, a mean duration of 69 seconds and a probability of recurrence of 0.43 (2). The underlying cause of hypoxemia is undetermined and may be multifactorial. Hypercapnia frequently accompanies hypoxemia, particularly with more severe desaturations (<85%) and may be prolonged (mean duration 424 seconds), despite post-ictal increases in the rate and depth of respiration (5). Hypoxemia and hypercapnia could potentially contribute to SUDEP through known effects of these disturbances on cardiac and cerebral function. Indeed, ictal hypoxemia has been associated with bradycardia, tachycardia, and cardiac repolarization changes (3, 6, 7), in addition to post-ictal generalized EEG suppression (8, 9) and post-ictal immobility (10). Other peri-ictal respiratory complications, such as obstructive apnea due to laryngospasm and neurogenic pulmonary edema, have also been observed in SUDEP and near-SUDEP (11). It remains to be determined how common peri-ictal respiratory accompaniments relate to the relatively rare occurrence of SUDEP, and this will be a focus of future research efforts.

SUDEP, SIDS and Serotonin

Presented by George B. Richerson, MD, PhD

It is not known how seizures cause respiratory arrest. This talk discussed animal experiments aimed at defining the mechanisms involved. The serotonin (5-HT) system has emerged as a potential target for more specific treatments because it appears to play a central role in respiratory dysfunction induced by seizures. For example, 5-HT2c receptor knockout mice develop spontaneous seizures followed by respiratory arrest, suggesting that defects in the 5-HT system can induce seizures and also have an independent effect to increase the risk of SUDEP (12). The DBA/1 and DBA/2 strains of mice have autonomic seizures and a high rate of post-ictal respiratory arrest (13). Treatment with a serotonin reuptake blocker reduces the incidence of respiratory arrest in a dose-dependent manner in DBA/2 mice (14), and in epilepsy patients these drugs are associated with reduced severity of oxygen desaturations during and after seizures (15). We have found that Lmx1b conditional knockout mice, in which >99% of 5-HT neurons have been genetically deleted (15), also have a decreased seizure threshold, as well as an increased incidence of respiratory arrest after seizures (16). The association of seizure-induced death in mice with defects in the serotonin system led to the suggestion that SUDEP may share mechanisms with sudden infant death syndrome (SIDS), which has many similarities. For example, both have been proposed to be due to respiratory, arousal or cardiac mechanisms, and both are more likely to occur when individuals are in the prone position (17). An increase in risk of SUDEP and SIDS due to defects in 5-HT neurons would not be unexpected, because 5-HT neurons in mice have been shown to be important for detecting an increase in blood carbon dioxide levels and causing an increase in breathing and arousal from sleep (18–20). Future experiments will seek biomarkers for defects in 5-HT and ways to reverse 5-HT abnormalities so breathing and arousal would not be inhibited so severely after a seizure.

Respiratory Rhythm Generation and Long QT genes

Presented by Daniel Mulkey, PhD

Mutations of some ion channel genes cause long QT syndrome (LQTS), an abnormality in the EKG associated with an increased risk of sudden death due to a cardiac arrhythmia. These genes are expressed in the heart, but many are also expressed in the brain. Some have more recently been linked to epilepsy and SUDEP. Many cases of SUDEP in these patients with LQTS mutations are probably due to seizure-induced cardiac arrhythmias, but it has recently been found that some LQTS ion channels are expressed in respiratory nuclei of the brainstem. This talk focused on the role of KCNQ channels in the retrotrapezoid nucleus (RTN), an area important for central chemoreception, and on how serotonin modulates KCNQ channels and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (21). Serotonin alters the activity of RTN neurons via 5-HT2 and 5-HT3 receptors that act on KCNQ and HCN channels, thereby affecting breathing. Mutations in these channels might make a person more susceptible to respiratory arrest if a seizure invades the brainstem. Defining what makes
the respiratory control network stable or unstable, and how it is affected by 5-HT, may lead to new targets for prevention of SUDEP.

**Adenine in the Brainstem**

Presented by Detlev Boison, PhD

Increased availability of the neuromodulator adenosine suppresses neuronal activity as an innate mechanism to stop seizures, but it also suppresses respiratory functions in the brainstem. This talk focused on the “adenosine hypothesis of SUDEP,” which predicts that a seizure-induced adenosine surge, in combination with impaired metabolic clearance, can trigger lethal apnea. If excessive adenosine triggers SUDEP, then adenosine receptor antagonists, such as caffeine, should prevent SUDEP. When acute seizures are triggered in mice with pharmacological block of metabolic adenosine clearance, all animals develop prolonged apnea and lethal outcome, whereas a single injection of caffeine given immediately after seizure onset significantly prolonged survival time (22). Similarly, in a mouse model of temporal lobe epilepsy in which spontaneous recurrent partial seizures were induced by an intra-hippocampal injection of kainic acid, there was a significant upregulation of the adenosine metabolizing enzyme adenosine kinase (ADK) in the nucleus tractus solitarius (NTS), likely a compensatory mechanism to protect the brainstem from excessive adenosine. Engineered mice with heterozygous deletion of the Adk gene and compromised metabolic clearance of adenosine were characterized by a milder seizure phenotype compared to wild-type littermates; however, 3 out of 8 mutants succumbed to sudden death, whereas none of 11 epileptic wild-type controls died. Histologically, the mutant epileptic animals had lower levels of ADK expression in the NTS compared to epileptic wild-type mice, suggesting that deficient metabolic clearance of adenosine can contribute to SUDEP in chronic epilepsy.

**Characterization of Respiratory Arrest-Susceptible DBA/1 TPH2-ChR2 Mice**

Presented by Hua-Jun Feng, PhD

DBA/1 mice, a model of sudden unexpected death in epilepsy (SUDEP), exhibit respiratory arrest (RA) leading to death after generalized audiogenic seizures (AGS). Studies suggest that a deficiency of serotonergic (5-HT) transmission may contribute to RA in DBA/1 mice. This talk focused on a new method of studying the pathophysiology of RA in this model. Transgenic DBA/1 mice that specifically express channelrhodopsin (ChR2) in 5-HT neurons (TPH2-ChR2) were created in preparation to studying the pathophysiology of RA in DBA/1 mice. This talk focused on a new method of studying the pathophysiology of RA in this model. Transgenic DBA/1 mice exhibit similar AGS and incidence of RA as wild-type DBA/1 mice. Our results also suggest the backcrossing strategy can be applied to study many other neurotransmission systems in these mice.

**Acknowledgments**

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**References**

In Sweden in 2008, 1,891 people with epilepsy died. A review of the cause of death (CoD) in this cohort revealed 163 (8.6%) potential epilepsy-related causes. Of these 163 cases, SUDEP was the cause in 65 (39.9%), but epilepsy was coded on the death certificate as the principle CoD in 15 (23%) and mentioned on the death certificate in 49 (75%). The history of epilepsy was never mentioned on the death certificates of 22 definite or 13 suspected suicides. Among all 1,891, epilepsy was mentioned on 285 (15.2%) death certificates.

Medical examiners and coroners play a central role in the surveillance of mortality in patients with epilepsy (1). Many deaths in people with epilepsy are sudden, unexpected, or unnatural. Natural causes include SUDEP or death during a seizure. Accidental causes include positional asphyxia, drowning, motor vehicle accident, and so on. Medical examiners determine CoD and manner of death, including careful exclusion of other causes (e.g., drug overdose, heart disease, etc.). The extent of investigation and specific coding vary widely by jurisdiction (2). There are federal efforts to standardize and improve surveillance. Approaches include flexibility and control of content and distribution of SUDEP information, and these does not require legislative action. Cons include time-consuming work, lack of surveillance, and inconsistent execution. The state medical examiner approach include flexibility and control of content and distribution of SUDEP information, as well as awareness efforts and the development of death investigator training programs.

References
is well known that many seizure types—especially generalized tonic–clonic seizures—are associated with suppression of awareness and decreased arousal. It is becoming recognized that these mechanisms may play a role in SUDEP. It is also becoming recognized that there is a time-of-day, if not sleep-state predilection for SUDEP, with a high percentage of SUDEP occurring at night and during sleep. The purpose of this session was to discuss possible roles of sleep and arousal systems in SUDEP. Two speakers addressed mechanisms by which seizures affect arousal and breathing through network interactions, and two speakers addressed neurotransmitter mechanism in mouse models—one discussing serotonin and one addressing adenosine, the two neurotransmitter systems that play a large role in regulation of both arousal and breathing. Finally, there was a presentation from the abstract winner investigating a role for sleep position in SUDEP.

Human Peri-Ictal Physiology: Central Shutdown and Arousal Systems
Presented by Hal Blumenfeld, MD, PhD

Through numerous electrophysiological and functional imaging studies in patients with epilepsy, Dr. Blumenfeld’s group has shown that seizures have long-range effects on cortical and brainstem structures (1). This is presumed to be through interactions with other local networks, a phenomenon dubbed “the network inhibition hypothesis.” Dr. Blumenfeld described a rat model that his group developed which can be used to study these long-range and network effects of seizures (2). New studies were described, demonstrating that in addition to monitoring effects of seizures on cortical systems, this model can also be employed to evaluate effects on brainstem arousal systems and respiratory control networks. In particular, changes in firing characteristics of neurons within serotonergic subnuclei were described. Should preliminary studies hold true, this important work will provide a functional mechanism for the hypothesis that seizure-induced arousal impairment and respiratory dysfunction that contribute to SUDEP involve dysregulation of the serotonin system.

Human & Mouse Mechanisms of Brainstem Invasion
Presented by Brian Dlouhy, MD

An elegant series of studies were described in which electrophysiological recordings were made from patients with epilepsy at baseline and then following direct simulation of the amygdala. In one patient, respiratory arrest and oxygen desaturation coincided with spread of the seizure into the amygdala. Respiratory arrest and oxygen desaturation could be reproduced with stimulation of the left or right amygdala. Stimulation outside of the forebrain did not cause respiratory suppression or oxygen desaturation. These studies lend important insights into the contributions of connections between the amygdala and respiratory control centers in the medulla to the influence of seizures on breathing, suggesting that similar mechanisms exist for the regulation of sleep and wakefulness following a seizure. This lays the groundwork for future studies to better understand mechanisms for respiratory consequences of seizures.

Serotonin and Post-Ictal Breathing and Arousal/Sleep
Presented by Gordon F. Buchanan, MD, PhD

Serotonin is an important regulator of sleep and wakefulness, and breathing. Levels of serotonin are decreased following a seizure, and anti-epileptic drug therapies affect serotonin levels (3). Serotonin can also modulate seizure control (4). Preliminary studies were described using the Lmx1b<sup>fl/fl</sup> genetic mouse model (5) in which nearly all serotonin neurons in the central nervous system were eliminated developmentally. These mice had previously shown to have impaired ventilatory and arousal responses to carbon dioxide (6, 7). They also have had increased sensitivity to seizure induction in a number of experimental models (8). Preliminary studies were presented, revealing that the degree of the effect of seizures on breathing may depend on the sleep state during which seizures occur. Preliminary studies also reveal that there may be impairment of CO<sub>2</sub>-induced arousal and ventilatory responses in the period immediately following the seizure, and that these impairments are serotonin-dependent. Understanding how sleep-state and nighttime interact with seizure occurrence in increasing the likelihood of SUDEP is likely to be important in devising strategies to prevent SUDEP.

Adenosine: Sleep and Post-Ictal Respiratory Arrest
Presented by Carl Faingold, PhD

DBA/1 and DBA/2 mice have proved to be important models for understanding seizure-related respiratory arrest and respiratory etiologies of SUDEP. Dr. Faingold’s group has used this model to demonstrate the importance of the serotonin system in seizure-induced respiratory arrest (9–12). Here, he described forays his group is making into understanding the role of another brain chemical—adenosine—in respiratory- and arousal-related etiologies of SUDEP using the DBA animal models. Adenosine, like serotonin, is involved in regulation of breathing and sleep and wakefulness, as well as modulating seizure control, making it an important candidate in mechanisms of SUDEP. Preliminary studies were presented that demonstrate that adenosine or blocking the breakdown of adenosine increases the proportion of animals that have seizure-related respiratory arrest, whereas blockage of adenosine receptors using drugs such as caffeine reduces the proportion of mice that have respiratory arrest after a seizure. Such studies have intriguing implications for future preventive strategies for SUDEP.

Abstract Presentation Winner

Association of Prone Position With Sudden Unexpected Death in Epilepsy
Presented by James Tao, MD, PhD

Drawing parallels to another sudden death phenomenon, sudden infant death syndrome (SIDS), Dr. Tao presented data from a meta-analysis in which he explored the possibility that at least part of the reason SUDEP tends to occur more often during the night has to do with sleeping position. The prone position increases the likelihood that the nose and mouth
could be obstructed and lead to blockage of airflow should this happen following a seizure. This is considered a major contributor to death in SIDS and instigated the "Back to Sleep" campaign still advocated today, recommending that all babies be put to sleep on their backs (13), and it seems also pertinent to SUDEP.

### References


### Session Summary: Non-SUDEP Deaths in Epilepsy

**Moderator:** Dale C. Hesdorffer, PhD

Epilepsy-related causes of death other than SUDEP affect many individuals, may occur unexpectedly and, in most cases, targeted prevention is absent. These deaths, due to status epilepticus (SE), acutely provoked seizures, suicide, antiepileptic drug (AED)-related cardiovascular disease, and adherence to AEDs comprise a second group of deaths, some of which may be preventable.

**Status Epilepticus and Acute Symptomatic Seizures**

Presented by Dale C. Hesdorffer, Ph.D.

Epidemiological studies have shown that 24% of people with a first episode of SE die (1). These deaths are 6-fold greater in people with acute symptomatic SE compared to those with unprovoked SE, and older people are 1.9-fold more likely to die. The cumulative risk for dying within the first 30 days after SE is greatest for acute symptomatic etiology, and there are no deaths in people with SE of unknown causes (2). Among 30-day survivors of SE, the 10-year mortality is highest in people with degenerative diseases (e.g., Alzheimer disease) compared to all other etiologies of SE (3). SE due to anoxic encephalopathy is associated with a 14-fold higher risk of death than other etiologies (4).

Death occurs in 9.5 to 37.3 percent of people with a first acute symptomatic seizure. In the first 30 days after a first acute symptomatic seizure (5), death is higher than in people with a first unprovoked seizure (6). The cumulative risk of dying within the first 30 days is 20% for acute symptomatic seizures (6), representing a more than 100-fold increase compared to the general population. The two etiologies with the greatest risk for death in the first 30 days are cerebrovascular disease, followed by encephalopathy (6). Among 30-day survivors of acute symptomatic seizures, the risk of dying over the next 10 years is 80%, a 10-fold increase over the general population (6). The etiologies with the greatest risk for death among 30-day survivors are traumatic brain injury, and alcohol and drug withdrawal. These etiologies are themselves associated with death without the presence of seizures.

**Occurrence and Risk Factors for Completed Suicide in Epilepsy**

Presented by Nathalie Jette, MD

Suicide is very rare in the general population. Assessing suicide in people with epilepsy, therefore, requires that sizeable populations be followed for 50,000 person-years or longer to obtain statistically significant results (7). Across studies, there is a 3.3-fold increased risk for suicide in people with epilepsy (8). Risk factors for completed suicide in people with epilepsy include neurodeficits present since birth, psychiatric illness, antipsychotic drugs, onset of epilepsy under 18 years, and alcoholism (9, 10). In a large Danish study, the increased risk for suicide in epilepsy has been observed in those without psychiatric disorders as well as in those with psychiatric disorders, where there is a 13.7-fold increased risk (9). Compared to men without epilepsy in this study, men with epilepsy had a 1.8-fold increased risk for suicide in the absence of a psychiatric disorder and a 9.9-fold increased risk in the presence of a psychiatric disorder. These estimates were appreciably greater in women with epilepsy (2.5- and 28.6-fold, respectively) (9). Among comorbid psychiatric disorders in people with epilepsy from the Danish study, the increased risk for suicide

20

Partners Against Mortality in Epilepsy Conference Summary
was greatest for mood disorder, followed by chronic alcohol use (9). In contrast, mood disorder and schizophrenia have the greatest increased risk for suicide in people without epilepsy. Among 1,877 Finish people who committed suicide, those with epilepsy were more likely to be female, less likely to have alcohol-related disorders, and more likely to have any psychiatric disorder (depression in particular) (11). It is important for clinicians taking care of people with epilepsy to identify psychiatric disorders, be familiar with risk factors for suicide in epilepsy, and work with psychiatrists to reduce the risk of suicide in epilepsy.

In 2009, the FDA issued a warning about the risk of suicidal thoughts and behaviors associated with antiepileptic drugs (12). Several observational studies conducted in large databases failed to provide further information due to methodological issues. Recently, a study from the VA system showed that the risk for suicide-related behavior was increased in the 2 months before AEDs were first prescribed and decreased after prescription, suggesting that AEDs were given and acted successfully as mood-stabilizing drugs (13).

**Cardiovascular Disease and Epilepsy/AEDs**

Presented by Scott Mintzer, MD

Epidemiological studies of epilepsy have shown statistically significant increased standardized mortality ratios for cardiovascular causes of death, including heart disease, stroke, myocardial infarction, and ischemic heart disease (14–20). AEDs that are strong P450 enzyme inducers (e.g., carbamazepine [CBZ]) appear to affect cholesterol synthesis. As such, they may have long-term effects on cardiovascular health, indexed by high levels of cholesterol as well as other markers. This hypothesis has been evaluated in more than 10 cross-sectional studies that have found that cholesterol is increased in patients treated with CBZ compared to controls or to patients treated with valproic acid (21). Other studies have shown elevated cholesterol in people on phenobarbital or phenytoin. However, these cross-sectional studies cannot elucidate time order of the association between the P450 enzyme-inducing drugs and elevated cholesterol.

In a study of epilepsy patients who were switched from P450 enzyme-inducing drugs to non-inducers, fasting measures of cardiovascular health were compared on the enzyme-inducing AED versus the non-enzyme inducer AED, six weeks after the last dose of the enzyme inducer AED (22). Statistically significant decreases were seen for total cholesterol, non-HDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, lipoproteins, and homocysteine. All changes in these values were statistically different from normal controls over the same time period. A Danish study examined the effect of AEDs on cardiovascular morbidity and mortality (20). Compared to CBZ, the risk for these conditions was lower on valproate, consistent with a potentially greater cardiovascular risk form CBA treatment. However, some of these other findings were not entirely consistent with this hypothesis.

These studies suggest that enzyme-inducing AEDs have deleterious effects on markers of vascular risk and possibly increase the risk for myocardial infarction and other vascular conditions. Screening for vascular risk in patients on enzyme-inducing drugs is needed, not only for epilepsy but also for patients given these drugs for mood stabilization. Further studies are needed to determine whether inducing AEDs increase the risk for the endpoint of vascular disease.

**Nonadherence to Antiepileptic Drugs and the Risk for Death in Epilepsy**

Presented by Daniel Friedman, MD

Medication nonadherence—not taking prescribed antiepileptic drugs as directed by the provider—is common in people with epilepsy. Over a 12-month period after starting AEDs, only half the patients maintain a greater than 80% adherence as defined by the medication possession ratio, the days of drug supplied by the pharmacy divided by the days in the observation period. Consequences of nonadherence include increased rates of seizure-related hospitalizations and emergency department visits, and higher costs associated with nonadherence in the elderly (23). Nonadherence is also associated with an increased rate of injuries and accidents, such as fractures and motor vehicle accidents (24). Most importantly, nonadherence to AEDs as prescribed is associated with a 3-fold increased risk of death (24).

Several SUDEP case series from medical examiner or coroners’ offices show a high frequency of low or absent AED levels, ranging from 46 to 94 percent (25–30). However, results from controlled studies are mixed. In a retrospective study of AED levels in hair samples assessed by high performance liquid chromatography, SUDEP cases had a greater variation in drug levels compared to controls (31). Postmortem toxicology studies have shown varied results; a study in the United States showed significantly more SUDEP decedents had low or no AED levels compared to non-SUDEP epilepsy decedent controls (69% vs 34%), whereas a study in Australia showed no difference in the frequency of subtherapeutic/absent AED levels between SUDEP cases and controls (52% in both groups). These studies differ from more methodologically sound investigations. In a nested case-control study performed at 3 epilepsy centers comparing 20 SUDEP deaths to 80 living controls with epilepsy, there was no difference in the degree to which the last known AED level was low (32).

Important questions that need to be further addressed are whether AED nonadherence is a modifiable risk factor and whether interventions might lower the risk of SUDEP and other causes of mortality in epilepsy. In considering whether nonadherence is modifiable, it is important to note that memory problems, insurance status, beliefs about medications generally, AED side effects, and psychiatric disorders may all contribute to nonadherence, making common interventions challenging toward improving adherence. Some potential ways to improve AED adherence include: pillboxes and text messages to improve remembering each dose; education and motivational interviewing to better understand the need for medication use; and patient–clinician collaboration to identify the best tolerated yet effective medication regimen. Further studies should examine risk factors for nonadherence toward selecting an intervention that would be most likely to improve AED adherence and reduce mortality in epilepsy.
References

Session Summary: SUDEP Mechanisms: Autonomic and Cardiac
Moderators: Jeffrey W. Britton, MD, Jeffrey Noebels, MD, PhD
Acute, transient modulations in cardiac function are common during seizures, and chronic changes in cardiac autonomic tone have been described in patients with intractable epilepsy. Seizure-induced disturbances in the central autonomic modulation of heart function can be significant and are a potential SUDEP mechanism. The influence of epilepsy on heart function is an example of a phenomenon referred to as the “heart–brain connection.” The heart–brain connection may have shared SUDEP mechanism. The influence of epilepsy on heart function can be significant and are a potential SUDEP mechanism. Examples of the latter include seizures and ventricular arrhythmia seen in patients with catecholaminergic polymorphic ventricular tachycardia due to RYR-2 mutations, and the existence of both...
epilepsy and cardiac phenotypes in long QT syndromes due to mutations in KCNQ1 and related genes.

This plenary session focused on the spectrum of central cardiac autonomic control and how it may be affected in epilepsy. Recent discoveries involving human and experimental models were presented, which may help shed light on the underlying physiologic abnormalities that may account for the increased prevalence of SUDEP.

**Overview of Central Autonomic Cardiac Anatomy and Physiology**

Presented by Jeffrey W. Britton, MD

Dr. Jeffrey W. Britton from Mayo Clinic in Rochester, MN, provided an overview of the central nervous system structures involved in cardiac autonomic modulation (1). A historical review indicated that seizures have been known to produce significant disturbances in central autonomic control of the heart for centuries. In the last 50 years, cortical stimulation studies in humans and animals identified the important roles of the insula, cingulate gyrus, orbital frontal regions, and amygdala in central autonomic modulation of the heart. These limbic regions are often affected by seizures.

Key brainstem structures participating in central cardiac modulation were highlighted, including those involved with sympathetic efferent function (rostral ventrolateral medulla), parasympathetic efferent activity (nucleus ambiguus, and dorsal motor nucleus of the vagus), and integration of afferent input from peripheral baro- and chemoreceptors (nucleus of the tractus solitarius) (2). He also reviewed the literature on the effects of neurologic lesions and seizures on heart rate variability (HRV)—a biomarker of the integrity of the baroreflex—where disturbances have been associated with sudden death. The effects of seizure-induced cardiac sympathetic and parasympathetic modulation were also reviewed. These included cardiac repolarization defects seen in the peri-ictal period, such as QT interval abnormalities, bradycardia, myoccardial ischemia, and Takotsubo, all of which could serve as potential SUDEP mechanisms.

**Patient-Derived Pluripotential Stem Cells and SCN1A Mutation Knock-In Mice Models of Dravet Syndrome**

Presented by Lori L. Isom, PhD

Dr. Lori L. Isom, University of Michigan Medical School in Ann Arbor, presented recent discoveries related to cardiac and neuronal pathophysiology in Dravet syndrome. She reviewed recent results of experiments performed on neural progenitor cells derived from induced pluripotential stem cells obtained from Dravet syndrome patients with defined SCN1A sodium channel mutations (3). These neurons showed increased sodium current density, reduced threshold for action potential initiation, and abnormal hyperexcitability firing patterns, including spontaneous burst activity.

She also presented experiments performed in cardiac tissue from knock-in mice heterozygous for an SCN1A mutation associated with Dravet syndrome (4). These demonstrated increased sodium current density in cardiac myocytes, and arrhythmias with repolarization defects including QT prolongation.

Collectively, these findings suggest that both neuronal and cardiac excitability are present in Dravet syndrome and could underlie the increased potential for SUDEP in these patients.

**Sodium Channel Deletion, Asystole, and Fatal Seizures in Murine Models of Dravet Syndrome**

Presented by Franck Kalume, PhD

Dr. Franck Kalume, from University of Washington in Seattle, presented findings from work involving Nav 1.1 channel knock-out models of Dravet syndrome. These mice are prone to sudden death during thermal-induced seizures. Decreased heart rate variability has been found in this model, which is a biomarker for sudden cardiac death (5). During thermal-induced seizures, Dr. Kalume noted that EKG monitoring showed significant bradycardia at seizure onset and offset in fatal seizures. Atropine blocked this response, suggesting parasympathetic hypertonia in affected cases. Based on these findings, he proposed consideration of inhibiting vagal input by modifying the function of a commercially available vagus nerve stimulator as a potential preventative treatment for these patients.

**Clinical Cardiologic Consequences of Seizures**

Presented by Rainer Surges, MD

Dr. Rainer Surges, from University Hospital in Bonn, Germany, presented a comprehensive overview of the spectrum of cardiac complications encountered in patients with epilepsy (6). Tachycardia occurs in more than 80% of seizures, suggesting that sympathetic excess is common in epilepsy. In contrast, he noted that bradycardia is thought to be present in only 6% of seizures, and 1% of patients. The role of seizure lateralization on the occurrence of ictal bradycardia has been the subject of much research in the past; bradycardia usually occurs at a point when bilateral seizure activity is present. In most cases of ictal asystole, the interruption is transient and resolves spontaneously, casting some doubt upon its role in SUDEP. The role of cardiac pacing to reduce asystole-related SUDEP risk was discussed. He also presented preliminary work that raised questions regarding a role of anticonvulsant treatment in the occurrence of cardiac conduction abnormalities during seizures, which he suggested was worth exploring in future studies as a potential risk factor for SUDEP.

**Acquired Cardiac Risk and Potential Cardioprotective Therapy**

Presented by Yi-Chen Li, MD

Dr. Yi-Chen Li, from Texas Children's Hospital at Baylor College of Medicine in Houston, reported the presence of EKG changes that arise early in an experimental pilocarpine-induced rat seizure model. These animals showed abnormal tachycardia induced by ventricular pacing, and beta adrenergic blockade lowered the rate and QTc interval. If recognized early, this strategy may be a potential intervention in selected patients.

**Conclusions**

The heart is affected by epilepsy, and some seizures may be detrimental to normal cardiac function, potentially contributing to sudden death. Mechanisms underlying the heart–brain
connection—ranging from acute and chronic seizure-mediated derangements of central cardiac autonomic function to shared molecular lesions—are likely to play a pivotal role in the occurrence of SUDEP. Elucidating the precise pathophysiology will be necessary to identify potential protective therapies.

**References**


**Summary of Session: Epilepsy and Grief**

**Moderator:** Jeanne Donalty

The Learning Objectives of this session were: 1) identify the typical stages of grief a bereaved adult will go through; 2) understand the basic differences between complicated and uncomplicated grief, and hallmarks to watch for that could signify complicated grief; 3) understand predisposing factors, both general and SUDEP/epilepsy mortality-related, that can lead to grief complications; 4) identify when or if a referral for grief counseling is needed; 5) have an increased awareness of specific national and community grief support resources, which can be referenced.

**Story of Loved One**

**Presented by Lisa Riley**

Lisa Riley’s son, Jordon Buisman, was diagnosed with epilepsy as a child. He was placed on anti-seizure medication and eventually went into remission. Upon graduating from high school, Jordon joined the Marines. At 22 years of age, Jordon began to have nocturnal seizures and again was placed on medication. Although his seizures were under control, he was forced to retire from active duty after his epilepsy diagnosis. Jordon enrolled in college and was seizure free for almost 16 months, when he had a seizure while talking on the phone with his mother. He immediately contacted the VA for an appointment but was unable to get one for several months. Jordon died of SUDEP on November 26, 2012, weeks before his scheduled appointment. He was 24 years old. Since her son’s death, Lisa has struggled with severe depression and grief. She has sought professional help for both her emotional and physical issues. On the first anniversary of Jordon’s death, Lisa made a PSA to honor her son’s memory and increase awareness of SUDEP. Lisa now regularly speaks out about SUDEP and epilepsy to help deal with her grief in a positive way.

**From Normal to Pathological Grief: Recognition of the Pathogenic Mechanisms**

**Presented by Andres Kanner, MD**

Normal grief, found in the majority of survivors, is unique to each individual but often includes feelings of intense sadness, protest emotions, rumination about the loss, insomnia, poor appetite, and weight loss. As an individual begins to readjust to the loss, the intensity of grief begins to decrease over time, and the individual begins to incorporate it into their life—who they are.

Complicated grief is defined by symptoms, duration, and intensity. The individual becomes incapacitated, exhibiting significant distress and functional impairment, including emotional numbness and the inability to feel pleasure. Complicated grief is defined as long lasting, six months or more, and is estimated to affect 3–25 percent of loss survivors.

What can physicians do to prepare families for a potential loss and the grief that follows? Let us consider when the first encounter with grief occurs, which happens when a person experiences his or her first seizure. At that point, the individual—as well as the whole family—faces a profound loss. It then becomes the physician’s responsibility to understand this loss and help the patient accept the diagnosis of epilepsy by going through the grief process. To ignore this responsibility regarding the consequences of the patient and family not accepting the loss and dealing with their grief can create many different and serious complications.

Patients and families need to understand that there are complications that come with a diagnosis of epilepsy, so they can prepare themselves and feel empowered. They should be asked whether or not they have accepted their diagnosis and what are their fears and concerns. The physician’s responsibility is to help get patients and their families to a place where they accept the diagnosis of epilepsy and its consequences.

In this context, physicians should discuss SUDEP. This issue should be brought up by the doctor. When a person experiences a tonic–colonic seizure, the first thing that comes to mind is that they are going to die. Doctors routinely talk about this with their patients, and this should be the case with SUDEP.

If patients and their families do not come to terms with their epilepsy, there is an increased risk of complicated grief.

**Grief Counseling or Not – Navigating the Grief Journey**

**Presented by Linda Coughlin Brooks, RN, BSN, CT**

Everyone who experiences the death of a loved one will be faced with grief and must learn to cope with it. Grief is normal, but society today does not offer us the time we need to grieve, nor does it understand the grief process. We are expected to “buck up” and move on quickly. There are specific stages of grief: denial, anger, bargaining, depression, and acceptance.

When normal grief becomes complicated grief, it may be time to seek professional help. Signs that it is time for a referral include 1) inadequate coping skills; 2) a sense of hopeless-
ness; 3) feeling disenfranchised, sudden or traumatic grief; 4) somatic issues or changes in physical health; 5) isolation from friends, family, or prior activities; 6) history of depression, mental illness, or suicide ideation; and 7) self-destructive behavior.

Physicians may be helpful in suggesting grief counseling or grief therapy to a patient’s family members when appropriate, when any of the aforementioned symptoms become evident. Grief counseling helps to facilitate the “tasks of mourning” in the recently bereaved so that the individual can better adapt to the loss.

Grief therapy helps to identify and resolve the conflicts of separation that preclude the completion of mourning tasks in individuals whose grief is chronic, delayed, excessive, or masked as physical symptoms.

Neurologists should not hesitate to make these referrals.

Making a Grief Support Referral: Resources and Recommendations

Presented by Paul Scribner, MSW, LCSW-C

As a physician or other health care provider, you are in an ideal position to provide helpful resource referrals to someone who is bereaved by the loss of a loved one to SUDEP or another epilepsy-related cause. To be effective, however, you must:

1. Take time to understand some of the basic values, beliefs, and practices of the family that might impact how they deal with death and loss.

2. Have a researched list of trusted referral resources on hand. It is very important in working with a sudden death to understand and respect the views and wishes of the family. The more deeply you understand their unique needs, values, and rituals (familial, cultural, and religious) in relation to death and grief, the less likely you are to upset an individual or family, and the more effective you can be in helping them through a very difficult experience (1). The challenge is that it is not possible understand a family’s attitudes and rituals surrounding death without asking; very few families spontaneously offer the information. Below are few topics you might want to address in your initial assessment that can be woven into the conversation and help you better understand the sociocultural background of your patients and families and their beliefs (2).

By asking these questions, you will better understand their readiness for a referral, the best type of referral to make, and whether a referral is wanted or needed at this time. Here are some specific questions you might include:

- Mourning practices immediately following a death: “Are there some family traditions that are important to you in your grieving process?”

- Long-term mourning practices, either cultural or religious: “When you think about the next six months or a year, what kinds of things do you anticipate doing that are part of your family traditions or religious traditions or that will help you in the grieving process?”

- Funeral or memorial preferences: “What traditions will your family use to commemorate your loved one’s life after she dies?”

It is critical that you take time to prepare a list of go-to grief support resources now. It can take as little as an hour or two but will be well worth it the first time you have a bereaved family member walk in the door. The first step is to make sure you really understand your institution’s social work, counseling, and other grief support resources. If you do not have someone specifically trained in SUDEP and complicated grief issues, refer them to the resources on the SUDEP Institute’s website (3), where they can view trainings on SUDEP and complicated grief, download a bereaved information packet, and find other valuable resources.

Second, know the grief and loss resources in your local community. Most major metropolitan areas have at least one grief and loss center. Finally, be sure you have a list of the national organizations that provide list SUDEP-specific or grief-related support. Following is a list of organizations you should include:

### SUDEP Specific Organizations and Resources

1. Centers for Disease Control (SUDEP site)
2. Chelsea Hutchison Foundation
3. Citizens United for Research in Epilepsy (CURE)
4. Danny Did Foundation
5. North American SUDEP Registry (NASR)
6. Partners Against Mortality in Epilepsy
7. SUDEP Aware (Canada)
8. SUDEP Action (UK)

### Bereaved Parent or Grandparent Resources

1. Compassionate Friends
2. Mothers In Support and Sympathy (MISS Foundation)
3. AGAST: Alliance of Grandparents: A Support In Tragedy
4. Sudden Unexplained Death In Children Program (SUDC)
5. Griefnet.org

### General Counseling and Support Regarding Loss Resources

1. Association of Death Educators and Counselors (ADEC)
2. Local grief and loss centers in your community

### Medical and Investigative Resources

1. Centers for Disease Control and Prevention: SIDS and SUID
2. National Association of Medical Examiners (NAME)
3. International Association of Coroners and Medical Examiners
4. National MCH Center for Child Death Review

### References

Summary of Session: SUDEP Mechanisms – Genetics

Moderators: Daniel Lowenstein, MD, Alica M. Goldman, MD, PhD

The objective of the session was to provide an update on selected key advances in human and animal translational genetic research that inform our quest for precision SUDEP diagnostics, as well as an improved understanding of the molecular pathophysiology of the premature mortality in epilepsy.

Use of Genomics to Study Human SUDEP

Presented by Alica M. Goldman, MD, PhD

Identification of epidemiological risk factors has been instrumental in highlighting the societal burden of premature mortality in epilepsy and in identification of patient groups that have increased SUDEP risk (1, 2). However, the scope of individually predictive and actionable epidemiological factors is limited, and the personalized risk assessment will need to take into the account emerging knowledge about the SUDEP molecular mechanisms that appear to drive the complex cardiorespiratory compromise and are often accompanied by postictal generalized EEG suppression (PGES). The currently known candidate SUDEP genes are either associated with the control of respiration and arousal, or they are the molecules dually expressed within the neurocardiac and autonomic pathways (3). Detailed clinical, physiological, and molecular analysis of a child affected by Dravet syndrome who succumbed to SUDEP has uncovered a complex genomic pattern of de novo variants affecting the SCN1A and KCNA1 channels on the background of inherited variants in the cardiac arrhythmia and respiratory pathway genes (4). This case pointed toward the oligogenic molecular SUDEP risk reflective of the inheritance pattern previously observed in large-scale genetic investigations of human epilepsies (5, 6). Precision molecular diagnostic and prediction of individual SUDEP risk will necessitate research involving complex collaborative network of families, physicians, forensic pathologists, and basic and translational scientists, piloted by the STOP SUDEP registry and genetic repository and by the SUDEP Research Alliance sponsored by the National Institute of Neurological Disorders and Stroke (NINDS).

Lessons From EPGP and Epi4K

Presented by Daniel Lowenstein, MD, for the EPGP and Epi4K Investigators

As in other areas of neurology and medicine in general, one of the current great challenges in human genetics research is understanding the precise role of genetic factors in common forms of diseases that have a range of clinical presentations. This is certainly the case in the epilepsies, where major advances have been made in the identification of single gene mutations for epilepsy syndromes that have Mendelian patterns of inheritance, but the genetic basis of most nonacquired forms of epilepsy remain unknown (7). Twelve years ago, a group of us involved in epilepsy research met. Recognizing the rapid advances being made in genome sequencing technology, we committed ourselves to an international, collaborative effort to collect a very large cohort of carefully phenotyped individuals with specific forms of epilepsy. This led to the creation of the NINDS-funded Epilepsy Phenome/Genome Project (EPGP), which has now successfully identified more than 4,100 patients and family members—including almost 2,200 first-degree relatives—having either idiopathic generalized epilepsy or nonacquired localization-related epilepsy, as well as approximately 630 probands having either infantile spasms (IS), Lennox–Gastaut syndrome (LGS) or specific types of malformations of cortical development, along with both of their unaffected parents (8). Detailed phenotypic information on every participant—including fine details about seizure semiology, imaging, and electrophysiological studies—reside on a centralized, highly structured and mineable database, and blood samples have all been deposited at the NINDS Human Genetics DNA and Cell Line Repository at Coriell Institute for Medical Research (8).

The second phase of this effort, the genomic analysis of the EPGP cohort, is now underway. The Epi4K—Gene Discovery in Epilepsy Center Without Walls, also funded by NINDS, has a mission to identify the genetic risk factors that contribute to epilepsy and to discover tailored therapies for the treatment and prevention of epilepsy (9). Epi4K has four projects, and the first results from Project 1 (Epileptic Encephalopathies) has relied on the patients with IS or LGS collected in EPGP. Whole exome sequencing of 264 probands and their parents revealed nine genes with de novo mutations in two or more probands, including two (GABRB3 and ALG13) not previously associated with epileptic encephalopathies, with another 100 genes harboring a de novo mutation in single probands in genes ranked as relatively intolerant to mutations (6). We also found that the mutations were drawn preferentially from specific gene sets, including ion channels, genes known to cause seizures, autism or intellectual disability, and FMRP-regulated genes. Further sequencing of the rest of the EPGP cohort, as well as other epilepsy cohorts from around the world, is currently underway.

Key to the successes of EPGP and Epi4K has been the team’s breadth of scientific expertise, which includes almost 1,000 person-years of postgraduate training in more than 20 scientific disciplines, ranging from statistical genetics to pharmaceutical sciences to neurophysiology. The groups have also made an unambiguous commitment to collaboration, embodied by a detailed charter and publication policy that provides clear guidelines and expectations for all investigators. Among other things, the publication policy ensures that appropriate credit is given to the contribution of all members of the team and, in the case of primary papers, no individual is singled out as the first, senior, or corresponding author. For secondary papers, priority is always given to junior investigators for named authorship. Finally, the progress in EPGP and Epi4K has been driven by a clear focus on the patient as the prime beneficiary of these collective efforts, which engenders a commitment to do everything possible to accelerate the speed with which results can be generated and shared.

Isolating and Validating SUDEP Genes in Mouse Models

Presented by Jeffrey L. Noebels, MD, PhD

Patients with variety of epilepsies face unclear SUDEP risk. Identification and mechanistic understanding of genes predisposing to SUDEP is critical for the development of
personalized biomarkers, risk prediction, effective prevention, and development of novel therapeutic interventions. Discovery of SUDEP genes involves an iterative, hypothesis-driven process in which candidate molecules are identified in patients and animal models. They are then evaluated and analyzed in model systems using basic science techniques. The analysis commonly entails addressing several key questions related to the variant deleterious nature, penetrance, mechanism, biological impact, and therapeutic potential.

The first monogenic SUDEP models were mice carrying two independent deleterious human variants in the KCNQ1 gene associated with an inherited cardiac arrhythmia, so-called long QT syndrome (LQTS) (10). The gene was found to be unequivocally expressed in the heart as well as in cortical and subcortical brain structures, including the autonomic nuclei of the brainstem. Both Kcnq1 models displayed a “lock-step” phenomenon where the active interictal epileptiform activity frequently coincided with brief asytopic pauses seen in the electrocardiogram. The terminal SUDEP event was captured in both models. The animal SUDEP risk was validated by human studies. Johnson et al. showed that 25% of patients affected by LQTS due to KCNQ1 mutations had a history of a seizure phenotype (11). One of the first indications of complexities inherent to functional assessment of genetic variants came from a case report of a 12-year-old male afflicted by LQTS and seizures who died suddenly (12). Genetic screening uncovered a maternally inherited and functionally detrimental KCNQ1 variant that was believed to be benign based on bioinformatics analysis, yet it showed a prolonged QT without epilepsy in one parent. A “Type 2” SUDEP category involves genes dually expressed in the brain and autonomic nervous system but not the heart, such as the Kv1.1 ion channel (13). The channel was found expressed in the paranodal regions of the vagal nerve (14). Administration of the parasympatholytic agent atropine ameliorated the frequent interictal atrioventricular blocks observed in the Kv1.1 deficient mouse model (13), thus illustrating that therapeutic interventions in SUDEP are only one step away from understanding personal molecular make-up. Genetic mouse models also aid in uncovering novel genes with modulating effect on SUDEP risk, such the SENP-2 molecule that is a modifier of potassium channels (Yeh, 2014 submitted) or MAPT

**Sodium Channel Mutations and SUDEP**

Presented by Miriam Meisler, PhD

The sodium channel gene SCN1A has been extensively studied with relationship to Dravet syndrome, and mouse and human data have shown that de novo loss of function mutations in this gene are linked to SUDEP (4, 16–19). The SCN8A gene is a closely related paralog that is localized at the axon initial segment where it regulates the initiation of the action potential (20). SCN8A has documented roles in epilepsy, cognitive impairment, and SUDEP, as evidenced by mouse models and human data (21–24). The sodium channel gene family contains 10 evolutionary related genes encoding the large transmembrane pore forming α-subunit of the voltage-gated sodium channels (22). The SCN8A channel was the first SUDEP gene discovered by next-generation whole genome sequencing of the nuclear family of a proband affected by infantile epileptic encephalopathy and SUDEP (23). The de novo variant c.5302A>G (p.Asn1768Asp) altered an evolutionarily conserved residue in the Nav1.6 channel, and subsequent analysis of the biophysical properties of the channel demonstrated a large increase in persistent sodium current. Current-clamp analysis in hippocampal neurons transfected with p.Asn1768Asp mutant channels revealed increased spontaneous firing and paroxysmal depolarizing shift-like complexes, consistent with a dominant gain-of-function phenotype in the heterozygous proband. There has been rapid progress in techniques for generation of animal models, and TALEN and CRSPR/Cas are currently the leading technologies. We used TALENs to generate a mouse model carrying the missense mutation p.Asn1768Asp in murine Scn8a (25). The knock-in mouse model recapitulates the phenotype of severe, early onset seizures, and SUDEP. Video/EEG analysis detected ictal discharges that coincide with tonic seizures, generalized tonic–clonic seizures, and myoclonic jerks. Prior to seizure onset, heterozygous mutants were not defective in motor learning or fear conditioning but did exhibit mild impairment of motor coordination and social discrimination. This new mouse model provides a unique opportunity to evaluate the pathophysiological role of SCN8A in the mechanism of SUDEP.

**Abstract Winner Presentation: Modeling SUDEP and Stress in Genetically Epilepsy Prone Rats (GEPR-9s)**

Presented by Srinivasa Komajosyula

GEPR-9 rarely die as a result of their seizures and are thus an optimal model system to study environmental influences on seizure-related death. Postictal surge in adenosine has been implicated in the electro-clinically evident postictal generalized EEG suppression (PGES) (3, 26). Pretreatment of GEPR-9 with adenosine receptor blockers lead to prolonged postictal depression and hypoxemia and a seizure-induced death rate, thus providing supporting evidence for adenosine contribution to the epileptic seizure-related lethal cascade. One of the many effects of alcohol is alteration of the brain’s adenosine level (27). Alcohol withdrawal was used to model an environmental stressor triggering increase in the brain adenosine levels, and rats exposed to alcohol withdrawal exhibited an increase in seizure-related death rate. These experimental findings offer preliminary explanation for the observed increased SUDEP risk in epilepsy patients with a history of alcohol use (1).

**Summary**

Novel genes and biological pathways are being identified and next-generation platform will speed up the rate of their discovery. A focused, collaborative network involving patients, families, interdisciplinary experts, and basic and translational researchers is essential for progress in understanding SUDEP mechanisms and in the development of appropriate diagnostic and preventative strategies. Detailed ascertainment of patients will be critical for meaningful association of the genotype with the appropriate phenotype. Careful validation of uncovered genetic variation, together with forward and
reverse analysis of the gene function in model systems, will be critical for meaningful translation into clinical practice.

References


Session Summary: What Organizations Are Doing to Promote Understanding of SUDEP

Moderators: Jeffrey Buchhalter MD, PhD, Cyndi Wright, BS

The major advances in medicine that have occurred within the last few decades have been the result of careful clinical investigation and basic science discoveries from the laboratory. We need to acknowledge, however, that much of the motivation and funding for these discoveries comes from the communities of people who suffer the specific illnesses. In the case of epilepsy, this community is comprised of those who are bereaved from loss of a loved one (i.e., SUDEP) and those affected by seizures as part of their daily lives. A variety of organizations representing different constituencies have been established that advocate for those living with epilepsy in general and those who are bereaved. The reality that SUDEP is a common cause of mortality associated with epilepsy—especially when seizures are refractory to available therapies—has spawned the existence of several organizations to educate patients and professionals, support those who have lost a loved one, raise awareness in society, and lead the efforts to prevent this tragedy. In this session, we recounted the origins and activities of those organizations.

In 1995, five women in England joined together to create Epilepsy Bereaved. During the first 10 years, they motivated an international workshop on SUDEP (1996), the first national register of epilepsy-related deaths (2002), as well as national pathology (2003) and clinical (2004) guidelines regarding the reporting and discussion of deaths related to epilepsy. In recognition of the advances made thus far, the name of the organization was recently (2013) changed to SUDEP Action (1), the activities of which include: providing information, offering support, involving stakeholders, sponsoring research, and capturing data via the Epilepsy Deaths Register.

The late 1990s also saw the beginning of SUDEP-related activities in Australia. These efforts involved increasing awareness via the media, providing information to epilepsy-related websites, presentations to professionals (nurses and physicians) and members of Parliament. In 2005, the first edition of “SUDEP: A Global Conversation” (2) was published by Epilepsy Australia and Epilepsy Bereaved. This unique collection of essays provides a description of the experience of SUDEP and issues around mortality and epilepsy in a manner that is accessible to all individuals—patients, families, health care professionals, as well as advocacy organizations and governmental agencies. The second edition in 2011 added SUDEP Aware and the International Bureau of Epilepsy as partners.

The effort spread to North America in 2008 with founding of SUDEP Aware (3) in Canada. This small nonprofit organization created the first SUDEP specific online information repository, provided support services options for those affected by SUDEP, and introduced families to the possibility of participating in research. As part of a collaborative awareness campaign (4), user-friendly brochures were created for patients and family members of different ages that were made available, free online and in print.

The SUDEP Institute (5) was created within the Epilepsy Foundation in 2013. The activities of this relatively new organization have been extensive and include: 1) SUDEP education and awareness programs for lay and professional audiences, 2) drives and support for research efforts, 3) a support network providing counseling and community resources, and 4) coordination with other epilepsy organizations to enhance knowledge of SUDEP. The SUDEP Institute has sponsored webinars as well as an Infographic that has more than 100,000 views on social media. Most recently, the Institute has organized the incorporation of the medical examiner and coroner communities in the effort to better ascertain the occurrence of SUDEP.

The power of individuals to enhance awareness and action is illustrated by the Danny Did Foundation (6). This foundation, created after the loss of a little boy to SUDEP, sponsors local educational and awareness efforts. In addition, it has sponsored, via fund-raising, several important research efforts involving seizure detection devices.

Finally, the Chicago-based Citizens United for Research in Epilepsy (CURE) has added SUDEP to its portfolio of important research initiatives (7). CURE has funded several key discoveries regarding the pathogenesis and epidemiology of SUDEP, including: 1) the potential primary respiratory basis of SUDEP and intervention via serotonin uptake inhibitors, 2) potential cardiac etiology of SUDEP via physiology similar to the long QT syndrome, 3) creation of several mouse models of SUDEP, and 4) establishing tonic–clonic seizures as a clear risk factor for SUDEP. In addition, CURE has been an active collaborator in national and international SUDEP education and research activities with the National Institutes of Health and Centers for Disease Control and Prevention.

In summary, the last two decades have witnessed a tremendous international effort to increase awareness, education, and research into the most devastating consequence of seizures, SUDEP. Marked gains have been made by organizations founded by individuals who have rallied human and financial resources to prevent this tragedy to the greatest degree possible in future years.

References


Summary of Session: SUDEP – Devices, Treatment & Prevention

Moderator: Elizabeth J. Donner, MD, FRCPC

Overview

The last decade has seen a significant increase in research aimed to unravel the mystery of SUDEP. As teams work toward
an understanding of why and how SUDEP occurs, prevention remains the most critical goal of all SUDEP research. At present, risk reduction is the best approach to prevention. Given that the occurrence of frequent generalized tonic–clonic seizures is the best-described risk factor for SUDEP, any therapy that reduces the frequency of seizures may reduce SUDEP risk. Further, by modifying other risk factors—such as longer duration of epilepsy, poor adherence to treatment, and reducing the comorbidities of epilepsy—these therapies may reduce both overall mortality in epilepsy and SUDEP. Studies of surgical populations have demonstrated lower all-cause mortality in patients who are seizure-free following epilepsy surgery (1), and comparisons of SUDEP rates among people with epilepsy who received epilepsy surgery and those who did not have demonstrated higher SUDEP rates among those who have received surgery (2, 3). However, these studies cannot account for the inherent differences between people who are considered candidates for epilepsy surgery and those who are not.

In this session, we explored beyond the role of traditional epilepsy therapies, considering seizure detection devices, bedside interventions, supervision, and behavioral modification for the prevention of SUDEP.

**The Accuracy and Clinical Utility of Devices**

Presented by Daniel Friedman, MD

An effective device for seizure detection offers the possibility for caregivers to be alerted soon after seizure onset to deliver interventions that may shorten the seizure or minimize harm. Dr. Daniel Friedman, Assistant Professor of Neurology at the New York University – Langone School of Medicine, explained that such devices use one or a combination of detection methods to identify a seizure. Many seizures, especially tonic–clonic seizures, are associated with characteristic motor activity. Non-invasive sensors, such as accelerometers or surface electromyography electrodes, can be incorporated into devices worn by the person with epilepsy to detect seizure-related motion. Mattress motion or video motion detection devices can be used to identify nocturnal seizures. Monitoring for motion is relatively non-invasive and less costly than other methods; however, this approach is mostly limited to convulsive seizure and may be further limited by where the sensors are placed (mattress sensors in the bed, or video sensors in certain rooms). Devices may also use physiological parameters such as heart rate, pulse oximetry, and electrodermal activity to detect changes characteristic of seizures. Physiological monitoring may be more invasive than motor-only monitoring but provides the opportunity to focus detection on seizures with a higher risk of danger, such as those with persistent hypoxia.

Among the challenges in the development of seizure detection devices is the need to establish a balance of optimal specificity and sensitivity. While it is important that a device not miss a critical seizure (particularly if caregivers are relying on these devices as their only method of being alerted to a seizure), it is equally important to minimize false positive alarms that can have a significant negative effect on the quality of life of both the caregiver and person with epilepsy. Both motor activity and physiologic characteristics may lack specificity for seizures, resulting in high false positive alarm rates.

**Monitoring Devices: What to Know and What to Ask**

Presented by Tom Stanton

At present, several devices are commercially available in North America for detection of seizure-related motion, and other devices are under development. Tom Stanton, Executive Director of the Danny Did Foundation, outlined an approach for families when considering a device for seizure detection at home. He suggested that families speak with the treating physician to determine whether a device would be useful and appropriate; specifically, which type of seizures are most important to monitor, whether there are concerns about specific physiological parameters, and whether data from a device would be of use to the physician in making treatment recommendations. Other considerations for families and people with epilepsy include the cost of devices and the comfort and feasibility of device use. The role of devices for individuals with epilepsy who live alone remains a challenge for device developers.

Dr. Friedman and Mr. Stanton agreed that no seizure detection device has been proven to prevent seizures or SUDEP. There is some evidence from a study of deaths occurring in Epilepsy Monitoring Units that earlier resuscitation by a health care worker following seizure-related asystole increases the chances of successful resuscitation (4); how this translates to the community setting and the use of seizure detection devices is not known. Whether the fatal cascade that follows some seizures can be terminated is not clear. Further, it will be difficult to obtain definitive data to support any device as a SUDEP prevention tool, given the rarity of SUDEP and the large number of subjects required for such a trial. As such, the role of devices in SUDEP prevention remains difficult to establish.

**Nocturnal Supervision and Peri-Ictal Stimulation**

Presented by Lisa Bateman, MD

The relationship between sleep and SUDEP is intriguing. The observation that SUDEP occurs most frequently at night or in bed is longstanding, and people with nocturnal seizures have been shown to be at higher risk of SUDEP (5). Dr. Lisa Bateman, Associate Professor of Neurology at Columbia University, identified how sleep may contribute to SUDEP risk. Most often, SUDEP follows a convulsive seizure and, in many epilepsies, seizures are more likely to occur from sleep; such seizures are more likely to secondarily generalize (6). Sleep may also affect autonomic function, resulting in altered cerebral autoregulation in response to seizure-related hypoxemia, hypercapnia, and reduced heart rate variability (7).

Environmental factors may also contribute to an increased SUDEP risk at night, when people with epilepsy are more likely to be alone and unsupervised. The role of nocturnal supervision has been explored in limited literature. A study of SUDEP deaths among a cohort of young people with epilepsy and learning difficulties at a United Kingdom residential school found that all deaths occurred while students were away from the school, suggesting a protective effect of the more supervised school environment (8). A case-control study of 154 SUDEP deaths found nocturnal supervision (defined as room-sharing or the use of an auditory monitor) to be protective for SUDEP (9).
The benefits of supervision are likely tied to an intervention, yet the optimal intervention for SUDEP prevention has not been established. Dr. Bateman, in collaboration with Dr. Masud Seyal, reviewed the effects of nursing interventions, administration of supplemental oxygen, oropharyngeal suctioning, and patient repositioning on potential SUDEP biomarkers. Earlier peri-ictal interventions were associated with reduced respiratory dysfunction, postictal EEG suppression, and shorter seizure duration (10). Further studies using established SUDEP biomarkers are required to identify the role for interventions in both hospital and home settings. Studies of interventions to prevent SUDEP will face the same challenges as those for evaluating the effect of devices due to the infrequency of deaths and the large number of study subjects required.

Behavioral Modification
Presented by Martha Sajatovic, MD

Epilepsy self-management encompasses the skills a person with epilepsy uses to optimize their treatment adherence, control seizures and their consequences, and manage the effects of epilepsy on daily life. Dr. Martha Sajatovic, Professor of Psychiatry and Neurology and Willard Brown Chair in Neurological Outcomes at Case Western Reserve University, described the significant impact of formal epilepsy self-management programs on the mental health comorbidities of epilepsy. The Managing Epilepsy Well Network has demonstrated the effect of e-Health in the support of epilepsy self-management and maintains a complement of MEW e-Tools to complement self-management practices (11).

SUDEP Prevention from a Public Health Perspective: Changing Behavior
Presented by Tanya Spruill, PhD

Given the established link between poorly controlled seizures and SUDEP, optimization of epilepsy self-management may be a powerful risk-reduction technique. Dr. Tanya Spruill, Assistant Professor of Population Health and Medicine at New York University – Langone School of Medicine, described the behavioral risk factors that may affect seizure control and contribute to SUDEP, such as sleep deprivation, alcohol use, and AED nonadherence. Among these, AED nonadherence has been strongly linked to an increase in all-cause mortality in epilepsy (12). Nonadherence may take many forms: failing to fill prescriptions, omitting medication doses or taking extra doses, and taking medications at the wrong time or with prohibited foods or medications.

Well-designed strategies to improve AED adherence target modifiable patient-level adherence barriers, such as memory difficulties, depression and anxiety, pre-existing negative feelings about medications, lack of social support, and low self-efficacy. Dr. Spruill explained that patient education alone is not sufficient to improve nonadherence and change behavior. Tailored patient education tools should be used in combination with memory aids and reminders, social supports, and approaches such as motivational interviewing to obtain maximum effect.

Conclusion
As we consider preventative strategies for SUDEP, it is important to remember that the best way to reduce SUDEP risk is to reduce seizure frequency. While we await the development of devices and interventions targeted to reduce mortality, it remains imperative that all people with epilepsy work with their health care providers to reduce the burden of seizures. Epilepsy self-management tools should be combined with AEDs, and when seizures continue despite medical management, people with epilepsy should be referred for surgical evaluation. Finally, talking about SUDEP to people with epilepsy (including assessing risk and how to reduce that risk) is an important tool in the fight to save lives. Only when people with epilepsy are fully informed of the risks of their disorder can they actively pursue strategies to reduce their risk and prevent SUDEP.

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today's Date: 2014-08-22

2. First Name  Buchhalter     Last Name Jeffrey  Degree MD, PhD

3. Are you the Main Assigned Author?  ☒ Yes  ☐ No
   If no, enter your name as co-author:

4. Manuscript/Article Title: PAME Supplement Editor

5. Journal Issue you are submitting for:  14.6s

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
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<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
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<td>2. Consulting fee or honorarium</td>
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<td>3. Support for travel to meetings for the study or other purposes</td>
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<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
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<td>5. Payment for writing or reviewing the manuscript</td>
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<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
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<td>7. Other</td>
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* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
### Section #3 Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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<td>6. Payment for lectures including service on speakers bureaus</td>
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<td>10. Payment for development of educational presentations</td>
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<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
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<td>Yes</td>
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<td>Medical Economics Committee meeting</td>
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<td>13. Other (err on the side of full disclosure)</td>
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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☒ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:
Thank you for your assistance.
*Epilepsy Currents* Editorial Board