



SUDEP: Advances and Challenges

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Commentary on: Sperling MR.

Sudden Unexplained Death in Epilepsy. *Epilepsy Curr.* 2001 Sep;1(1):21-23.

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During the past 2 decades, lay and academic awareness of sudden unexpected death in epilepsy (SUDEP) has increased tremendously, generating much discussion and research. In looking back, we tend to focus on progress, and there has been much. But we should also focus on roadblocks and failures. Patients with epilepsy and their families, as well as neurologists and medical examiners, are much more familiar with SUDEP than they were in 2000. Research has exploded. Between 1970 and 2000, the National Library of Medicine (PubMed) identified 109 articles on SUDEP. In the subsequent 20 years, more than 1300 additional articles were published, an increase from 3.6 to 65 articles/year. Yet, our challenges remain larger than our successes. We do not understand why some seizures are fatal while others are not; why some succumb to SUDEP after a few seizures and others survive hundreds of similar seizures; we lack validated SUDEP biomarkers and accurate serial incidence data from large populations; we have yet to initiate an interventional SUDEP prevention trial, and we have not reduced health care disparities that increase epilepsy-related mortality. Paradoxically, these challenges prevent us from knowing if any of our successes have led to a reduction in the SUDEP rate.

Reflecting the current situation, this commentary is organized into 3 parts: (1) the big picture—how have our fundamental concepts about SUDEP changed? (2) what have been the major advances in SUDEP research and preventive strategies, and (3) what challenges remain?

The Big Picture

Mike Sperling's 2000 *Epilepsy Currents* review of SUDEP provided an excellent overview, including definitions, epidemiology, clinical risk factors (treatment-resistance, generalized tonic-clonic seizures, frequent seizures, nonadherence, polytherapy), and our lack of understanding about pathogenesis, other than that SUDEP often occurred shortly after a

convulsion and that cardiac (arrhythmias and structural abnormalities) and respiratory (central apnea) mechanisms were hypothesized.¹ He wisely recommended to seek complete seizure control, since even rare seizures increase SUDEP risk.

What has changed? Epidemiological studies confirmed earlier findings (eg, patients with frequent convulsions are at high risk), but refined our understanding. Children with epilepsy were thought to be at very low risk, but studies in Sweden and Ontario suggest their SUDEP rates are very similar to adults.^{2,3} And while patients with severe forms of epilepsy are at higher risk, those with fully controlled or fairly well-controlled seizures make up the large majority of people with epilepsy and comprise an important fraction of SUDEP cases.⁴ The observation that ~90% of SUDEPs are unwitnessed has been confirmed and led to the recognition that monitoring and providing basic first aid, especially during sleep, may be life-saving.⁵ Mechanistically, the pendulum swung from the seizure-induced cardiac arrhythmias and cardiac fibrosis to the postictal impairment of brainstem function leading to deficits in arousal, reflex responses to hypercapnia, and respiration. The pendulum has swung again, with brain–heart and brain–respiratory interactions rising in relevance.

Advances in SUDEP Research and Preventive Strategies

Family and Community Involvement: Need for Education

The rapid increase in SUDEP awareness and research was primarily instigated by devastated families who never heard about SUDEP, and by epileptologists seemingly powerless to predict or prevent these deaths. After the alarm was sounded, lay and professional organizations and national funding agencies mobilized. International collaboratives, such as the Partners Against Mortality in Epilepsy, were created to share information and perspectives. A paradigm shift occurred.



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Families wanted education about SUDEP before SUDEP. Every adolescent and adult patient and every parent of a child with epilepsy or an intellectually disabled adult with epilepsy must be informed. SUDEP education should not be restricted to those with uncontrolled seizures or a breakthrough convulsion after missed medications, sleep deprivation, or excess alcohol. We also need to learn how to effectively present information on seizure prevention and SUDEP, to systematically study gaps in how we educate people—for example, do they know what to do if they miss a dose of their daily medication, or suffer a gastrointestinal illness that causes vomiting or diarrhea and impairs medication absorption? SUDEP education is not something to consider, it is something to do, for all—a message endorsed by a growing number of epilepsy and neurology organizations, as well as public health agencies.

Reducing Seizures and Monitoring Can Save Lives

By 2000, strong epidemiological data showed that people with more severe and frequent seizures were at higher risk for SUDEP, suggesting that improved seizure control can save lives. Several lines of evidence support that improved seizure control is associated with reduced SUDEP rates—from placebo-controlled randomized antiseizure drug trials (lower SUDEP in active drug than placebo),⁶ as well as after epilepsy surgery,⁷ vagus nerve stimulation,⁸ or responsive stimulation therapies.⁹

Converging evidence supports basic first aid administered during, or shortly after, a convulsive seizure can be lifesaving.⁵ Rarely, deaths due to SUDEP have been recorded in epilepsy monitoring units and show that SUDEP most often occurs after a convulsive seizure in sleep in patients who are in the prone position and do not receive basic first aid.¹⁰ For adults with developmental disabilities who live in residential facilities, the probability of SUDEP inversely correlates with the degree of nocturnal monitoring.¹¹ No evidentiary line is definitive, but collectively they strongly suggest that nocturnal monitoring of people with nocturnal convulsions could save lives. Nocturnal seizures can be identified, and caregivers alerted, by watches that sense motion and/or electrodermal activity, arm monitors that detect electromyographic activity, and motion detectors under mattresses. Although we lack proof that they will prevent SUDEP, they are reasonable strategies as we await more evidence; however, they should not be considered infallible.

The Genetics of SUDEP

Despite the revolution in next-generation sequencing, genetic risk factors for SUDEP remain elusive. Although some genetic disorders that cause severe epilepsy (eg, some epilepsies associated with changes in *SCN1A*, *SCN8A*, Dup15q) are associated with higher SUDEP rates, this may simply reflect their severe epilepsy. Preliminary studies suggest that SUDEP victims have higher rates of pathogenic or potentially pathogenic variants in genes that affect neuroexcitability and cardiac rhythmicity.^{12,13}

Lessons From Basic Science

The number of animal models of SUDEP has expanded greatly in recent years, and with them, the number of potential mechanisms and anatomic structures implicated in SUDEP pathogenesis. The central autonomic network's cortical (eg, amygdala, insula) and brainstem (eg, dorsal motor nucleus of the vagus, pre-Botzinger complex) structures are implicated in several animal models. A Dravet mouse model of SUDEP reveals that death often follows a convulsive seizure and is associated with parasympathetic hyperactivity.¹⁴ Other animal studies have shown waves of depression¹⁵ or active seizure¹⁶ spreading to brainstem regions that control autonomic functions, including respiration. Animal models also implicate serotonin and adenosine neurotransmission in pathogenesis.¹⁷

Biomarkers

There is no validated biomarker of SUDEP risk. Postictal EEG suppression (PGES) has emerged as the lead biomarker candidate and mechanism (brain shutdown).¹⁸ The landmark MORTEMUS study showed that SUDEP occurs postictally and is accompanied by impaired respiration and arousal and bradycardia.¹⁰ The risk of PGES is increased for generalized tonic-clonic seizures with bilateral and symmetric tonic arm extension, occurrence in sleep, and lack of oxygen administration.¹⁹ Thus, even cellphone videos of convulsive seizures may help physicians stratify SUDEP risk.

Biomarkers will be essential to identify high-risk populations for clinical intervention trials to prevent SUDEP. The relatively low rate of SUDEP in the general epilepsy population would require a very large cohort followed for many years to be sufficiently powered—an expensive exercise. Further, biomarkers can lead or mislead: total cholesterol and low density lipoproteins were considered solid biomarkers of heart disease and sudden death risk based on epidemiological and clinical data from thousands of patients, but validation has been challenging for heart disease and absent for sudden cardiac death.²⁰

Health Care Disparities

Sadly, health care disparities for epilepsy extend to SUDEP: rates are higher for those from lower socioeconomic communities and those with comorbid psychiatric disorders.^{21,22} Among young adults in Ohio from low socioeconomic communities, epilepsy is associated with a 17-year reduction in life span—more than twice the reduction in moderate to heavy smokers.²³ For individuals with epilepsy who face disparities related to ethnicity, income or other factors, reducing those disparities can likely reduce the morbidity and mortality of epilepsy.

Epilepsy-Related Deaths: More Than Just SUDEP

Excess morbidity and mortality of epilepsy is not limited to SUDEP, but include drownings, motor vehicle accidents, falls, burns, and therapeutic complications.²⁴

Unmet Needs and Ongoing Challenges

We have many unanswered, basic questions. What causes SUDEP? Can we predict an individual's risk? Can we identify genetic, physiological, or other biomarkers of SUDEP risk? What aspects of seizures in sleep make them more deadly? Do seizure-detection devices reduce SUDEP risk? Do education and strategies to prevent seizures reduce SUDEP risk? When will we undertake a randomized trial to assess whether an intervention can reduce the rate of SUDEP? How do we reduce the health care disparities that make many more vulnerable to SUDEP and other epilepsy-related deaths?

Research should focus on these and other unanswered questions. We need to build upon our gains. We endorse that patients and families have a right to know about SUDEP, for example, informing a college student that missing medications, binge drinking, and sleep deprivation can cause convulsive seizures and increase SUDEP risk. How best to communicate this message so it changes behavior?

As we look to the future, we need answers. To get there, we will need to strengthen international collaborations that efficiently pool resources and focus efforts on understanding, prediction, and prevention.


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