Sudden Unexpected Death in Epilepsy

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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

Note from the Publisher

This publication has been developed without involvement of or review by the American Board of Psychiatry and Neurology.

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Sudden Unexpected Death in Epilepsy

William P. Cheshire Jr, MD, and William O. Tatum, IV, DO

INTRODUCTION

Epilepsy not only impairs quality of life but also carries an increased risk for premature death. Physicians who care for patients with seizures would benefit from greater knowledge of the syndrome of sudden unexpected death in epilepsy (SUDEP). Identification of patients at risk and factors relevant to prevention can be useful toward increasing epilepsy patients’ chance of survival.

DEFINITION

SUDEP is defined as a sudden, unexpected, nontraumatic, nondrowning, witnessed or unwitnessed death while in a reasonable state of health in a person who has epilepsy with no other obvious or structural cause of death. Except for status epilepticus, which is considered an exclusion criterion, death from SUDEP may or may not coincide with a seizure. Its mechanisms are complex, incompletely understood, and very likely heterogeneous.

EPIDEMIOLOGY

Population-based studies have shown up to a threefold increase in overall mortality for persons with epilepsy as compared to the general population, much, but not all, of which is explained by underlying brain disorders, which comprise neoplastic, cerebrovascular, and developmental conditions. The most common cause of death in adolescents and young adults directly related to seizures is SUDEP, with as many as 5000 deaths annually in the United States. Estimates of the risk of SUDEP vary widely due to the difficulties of capturing all cases in epidemiologic studies, unwitnessed deaths, and differences in diagnostic criteria and in the types of populations under study. The incidence of SUDEP has been established by retrospective assessments of medical records and autopsy records. A population-based study in Rochester, Minnesota, found that the incidence of sudden unexpected death in the epilepsy population exceeded that in the general population by 24-fold, with an incidence of 0.35 per 1000 person-years. Reviews of cases that came to the attention of medical examiners have estimated a high incidence ranging from 0.9 to 2.3 per 1000 person-years, although this range may be less representative of the general population, as it was extrapolated from the assumed prevalence of epilepsy in the coroners’ catchment areas. The highest incidences of SUDEP have been found...
within the epilepsy population, with incidences among epilepsy cohorts ranging from 1.1 to 3.8 per 1000 person-years, and among drug-resistant patients referred to tertiary centers as high as 6.0 to 9.3 per 1000 person-years. The highest incidence is in the 20- to 40-year age-group. The incidence of SUDEP during long-term video-EEG monitoring was approximately 1.2 per 10,000 video-EEG monitorings in a large multicenter retrospective study.

Most cases of SUDEP involve terminal pathophysiologic mechanisms usually due to generalized tonic-clonic (GTC) seizures. Sudden unexpected death has also been described in the absence of an immediate seizure in persons with remote symptomatic epilepsy. Because death in most cases of SUDEP is unwitnessed, epidemiologic studies cannot practically distinguish with certainty the relative incidence of SUDEP with or without a seizure. It is clear, however, that SUDEP is not fully explained by the comorbidities of epilepsy. A large Danish population-based study found that, while having epilepsy was associated with a severely increased risk of sudden unexpected death (hazard ratio 27.6), even after adjusting for neurologic and psychiatric comorbidities epilepsy itself carried an increased risk of sudden death (hazard ratio 16.3).

**RISK FACTORS**

Because SUDEP is the leading cause of epilepsy-related death, predicting which patients are at greatest risk, the likelihood of occurrence, and what preventive measures can be implemented are principal targets for neuroscientists and epileptologists. Known risk factors for SUDEP have been identified from descriptive case series and cohort studies. These risk factors may be subdivided into those that are related to seizures, those that are associated with epilepsy treatment, and those that are based upon individual patient characteristics.

**Seizure-related risk factors** for SUDEP pertain to seizure frequency, type, and setting. Case-control studies have consistently found an increased frequency of seizures in the months preceding SUDEP (Table 1). The risk is especially high for patients with GTC seizures. A large Midwestern U.S. prospective study of 4578 epilepsy patients captured 20 cases of SUDEP and found that, whereas the risk for SUDEP was significantly increased when patients experienced more than 50 seizures of any type per month, when only GTC seizures were considered, the risk for SUDEP increased significantly for as few as 1 to 3 per month (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.8–30.5), with even higher rates for more than 3 per year (OR 8.1, 95% CI 2.2–30.0).

Patients with nocturnal seizures and with seizures that occur while being in bed may be at the highest risk for SUDEP. In a UK cohort of 154 cases of SUDEP, 90 were sleep-related, and those who died during sleep were more likely to have a previous history of nocturnal seizures. 

**Epilepsy therapy risk factors** consist of duration of treatment for epilepsy (those treated for more than 10 years), seizures requiring multiple antiseizure drugs (ASDs), and subtherapeutic ASD serum concentrations, whether due to noncompliance with ASDs or during physician-guided ASD transitions.

**Patient risk factors** consist of younger age (typically 20–45 years of age), male gender (a ratio as high as 7:4 has been reported), and African-American ethnicity. The most significant risk factors for SUDEP are the severity of epilepsy and the intensity of the seizures. In a series of witnessed
SUDEP cases, convulsive seizures were observed in 12 of 15 patients. The typical SUDEP patient is an individual in his or her 20s to 30s with chronic, drug-resistant, temporal lobe epilepsy (TLE) associated with GTC seizures that have not been controlled by a single ASD who is intermittently compliant with treatment.

Children appear to have a lower incidence of SUDEP than adults. Patients with intellectual disabilities, however, are more likely to die due to SUDEP as compared to patients with normal mental status and intelligence, which may reflect differences in the anatomical origin or symptomatic phenotype of seizures stemming from underlying brain injuries. Regardless of cognitive status, intervention should be directed toward seizure control.

Noncompliance with ASDs is often coupled with drug or alcohol abuse, all of which are additional independent risk factors for SUDEP. The importance of counseling patients to be compliant with medical treatment and to avoid substance abuse behaviors cannot be overemphasized.

Many SUDEP victims have been found dead in bed. Frequently they are found in a prone position, which suggests airway compromise. The unobserved patient who “crashes” into bed after imbibing too heavily is at greater risk, especially if a seizure occurs while sleeping unattended. When there is a pattern of binge drinking, providing counseling that emphasizes the reality of SUDEP may help serve as a reminder of the potential seriousness of substance abuse in the context of epilepsy management.

Another high-risk group is patients with symptomatic localization-related epilepsy. These are patients with a defined etiologic structural lesion in the brain. Such patients are at particular risk and may account for up to 70% of reports of deaths from SUDEP.

Approximately 1 in 100 patients with a symptomatic cause for their seizures will experience SUDEP, as

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**Table 1. Risk of SUDEP by Seizure Frequency**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>No. of SUDEP</th>
<th>Seizure Type</th>
<th>Seizure Frequency</th>
<th>OR for SUDEP</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al, 1999</td>
<td>Stockholm, Sweden</td>
<td>57</td>
<td>All</td>
<td>3–12/yr</td>
<td>7.21</td>
<td>2.52–20.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13–50/yr</td>
<td>8.64</td>
<td>2.88–25.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;50/yr</td>
<td>10.16</td>
<td>2.94–35.18</td>
</tr>
<tr>
<td>Walczak et al, 2001</td>
<td>Midwest, US</td>
<td>20</td>
<td>GTC*</td>
<td>1–3/yr</td>
<td>2.4</td>
<td>1.8–30.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;3/yr</td>
<td>8.1</td>
<td>2.2–30.0</td>
</tr>
<tr>
<td>Langan et al, 2005</td>
<td>London, UK</td>
<td>154</td>
<td>GTC</td>
<td>&gt;0 over past 3 mo</td>
<td>13.8</td>
<td>6.6–29.1</td>
</tr>
<tr>
<td>Hesdorffer et al, 2011</td>
<td>US, Sweden, Scotland, England</td>
<td>289</td>
<td>GTC</td>
<td>1–2/yr</td>
<td>2.94</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–13/yr</td>
<td>8.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13–50/yr</td>
<td>9.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;50/yr</td>
<td>14.51</td>
<td></td>
</tr>
<tr>
<td>Shankar et al, 2014</td>
<td>Cornwall, UK</td>
<td>48</td>
<td>All</td>
<td>Increased over past 3–6 mo in 91%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; GTC = generalized tonic-clonic; OR = odds ratio.

*Seizures of any type achieved statistical significance only when frequency exceeded 50 per month (OR 11.5, 95% CI 1.3–99.3).

**The study was a combined analysis of pooled data from 4 case series.
compared to only 1 in 1000 patients with epilepsy due to a genetic cause. When a focal structural lesion is discovered, as in TLE due to hippocampal sclerosis, the potential for SUDEP must be weighed against the risks of epilepsy surgery. Patients with TLE represent a particularly high-risk group.9,21,22 One reason is that many TLE patients are drug-resistant. Another possible reason, for which the epidemiological association to date is indirect, is the proximity of the temporal cortex to other regions of the brain important for autonomic regulation of heart rate, such as the insula.23 Whereas lesions in these areas can cause cardiac arrhythmias, there are at this time no direct data linking seizure-induced arrhythmias from these regions to SUDEP. Furthermore, the heart rate increase in nonclinical seizures is different for temporal versus extratemporal seizure onset, supporting the concept of autonomic involvement in temporal versus extratemporal lobe epilepsies.9,22 Right TLE patients may be at greater risk for SUDEP.24

An illustrative case at our center was that of a 29-year-old man who had drug-resistant right TLE. Magnetic resonance imaging demonstrated right mesial temporal sclerosis, and positron emission tomography, right temporal hypometabolism. Video-EEG monitoring disclosed right temporal spikes interictally and right temporal seizures with dyscognitive features with a right temporal onset. He was awaiting right amygdalohippocampectomy when, after not showing up for work one morning, he was found, alone, dead in bed, without physical evidence of apparent harm or external signs of having experienced a seizure.

Unfortunately, this case scenario is not unusual. Sleep appears to be an independent risk factor for SUDEP.25 One study of 109 patients with convulsions suggested that a significantly lower preictal heart rate present in patients with nocturnal grand mal seizures (GMS) as compared to that in pa-
tients with diurnal GTC seizures might serve as a predisposition to SUDEP.25 In a large multicenter retrospective evaluation of SUDEP in a controlled hospital environment, SUDEP occurred between the hours of 7:30 PM and 6:00 AM in all but one patient. The investigators attributed this diurnal pattern to more effective supervision and timely CPR available during the day than at night.9

ELECTROENCEPHALOGRAPHIC FEATURES OF SUDEP

The electroencephalogram (EEG) may disclose features that convey a greater risk of SUDEP. Ictal recordings have shown more robust changes in heart rate associated with temporal lobe seizures,22 which may be more pronounced in patients with right hemispheric lateralization on EEG.24 Peri-ictal decreased heart rate variability,26,27 postictal increase in T-wave changes on the electrocardiogram (ECG),28 and a longer duration of the EEG suppression29,30 following convulsive seizures have been found to correlate with a greater risk for SUDEP.

Prolongation of generalized suppression on the EEG (Figure) in the immediate postictal time frame has been examined as a possible predictive biomarker for SUDEP. In one study, for every second of EEG suppression beyond 50 seconds, the risk of SUDEP was increased by 1.7%, and when the duration of suppression was longer than 80 seconds, the risk quadrupled.31 Generalized EEG suppression was defined as the global absence of EEG activity greater than 10 µV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts. Postictal generalized suppression of the EEG has been shown to increase the adjusted odds ratio for SUDEP (OR 5.22, 95% CI 1.26–21.58, P < 0.05), and for each 1-second increase in the duration, the odds of SUDEP increases by a
factor of 1.7% (95% CI 1.005–1.027, \( P < 0.005 \)).\textsuperscript{31,32} Generalized suppression occurs in approximately 65% of adult patients with generalized convulsive seizures and has been reported in several monitored SUDEP and near-SUDEP cases.\textsuperscript{31,33,34} In the pediatric population, the terminal ictal pattern of generalized suppression is less frequent, occurring in only 8% of patients, but when prolonged it may indicate an increased risk for SUDEP.\textsuperscript{35} Postictal suppression of the EEG is, therefore, considered one of the primary EEG biomarkers for SUDEP. The duration of generalized suppression appears to be related to the tonic phase of the GTC seizure.\textsuperscript{36} However, the precise temporal relationship appears to be less consistent.\textsuperscript{28} It may also be a marker for cascading postictal autonomic dysregulation. Some authors have termed this generalized suppression “cerebral shutdown” to reflect the reduction in cerebral metabolic rate in hypoxemic brain tissue after a seizure that may be a potential marker of SUDEP.\textsuperscript{37,38}

The postictal generalized suppression of the EEG background occurs during periods of hypopnea following a GTC seizure, but it does not appear to be caused by peri-ictal cardiovascular autonomic instability or respiratory suppression. Oxygen desaturation duration and extent as well as peak end-tidal \( \text{CO}_2 \) elevation were more marked.
in patients with postictal suppression on EEG. These patients were significantly more likely to be motionless postictally, have a prolonged recovery, and to require resuscitative interventions.

It is important to note that, whereas some studies have found postictal suppression on EEG to be a risk factor for SUDEP, this association has not been universal. In fact, postictal generalized EEG suppression is not specific to SUDEP, but rather occurs in 27% to 82% of patients with GTC seizures who do not experience a fatal outcome. Generalized suppression is, therefore, generally regarded to be an independent EEG feature indicating global cerebral dysfunction, but its precise relationship to SUDEP remains to be determined. SUDEP is more likely to be explained by the convergence of additional intrinsic and extrinsic factors.

**POSTULATED MECHANISMS**

Efforts to define the pathophysiologic mechanisms of SUDEP have drawn from clinical observations, comorbidities, analogous phenomena in nonepileptic persons, electrophysiologic and genetic investigations, and postmortem examinations. One reason its mechanisms remain elusive is that most cases are unwitnessed.

A large international, multicenter study of mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS) captured from among nearly 134,000 video-EEG recordings 16 cases of SUDEP and 9 cases of near-SUDEP with detailed descriptions in 10. In all assessable cases, a seizure preceded the cardiorespiratory arrest. The seizure was GTC in all SUDEP cases and in 7 of the 9 near-SUDEP cases. The immediate postictal phase was characterized by a sequence of events consisting of rapid breathing (18–50 breaths per minute), generalized EEG suppression, and cardiorespiratory dysfunction during the first 3 postictal minutes. The cardiorespiratory signs were bradycardia with onset between 15 and 140 seconds, apnea with onset between 25 and 180 seconds, and finally terminal asystole between 20 and 190 seconds. Cardiopulmonary resuscitation was begun within 3 minutes in all 7 nonfatal near-SUDEP cases, one of which also required defibrillation. These findings help to elucidate the temporal relationships of EEG and cardiorespiratory factors and underscore the potential contributions of ASD withdrawal and suboptimal supervision to SUDEP.

**CARDIAC ARRHYTHMIAS**

An important line of investigation has been to correlate epilepsy with traditional ECG markers of sudden cardiac arrest. A community-based study found that persons with epilepsy in general had a threefold increased risk for sudden cardiac arrest (adjusted OR 2.9, 95% CI 1.1–8.0, \( P = 0.034 \)).

A cross-sectional, retrospective study of ECG patterns found that, controlling for medications, persons with epilepsy had higher baseline heart rates, longer PQ intervals, and more frequent QTc prolongation or early repolarization pattern in comparison to controls without epilepsy. Prolonged QTc and early repolarization pattern are established risk markers for sudden cardiac death in the general population. Long QT syndrome is an inherited or acquired disorder characterized by delayed cardiac ventricular repolarization reflected by abnormal prolongation of the QTc interval on the ECG. Severely prolonged QTc (male >450 ms, female >470 ms) predisposes to malignant ventricular tachyarrhythmias, especially polymorphic ventricular tachycardia (torsades de pointes), which can progress to ventricular fibrillation and sudden cardiac death.
Whereas baseline heart rate has been reported to be higher in patients with epilepsy, and ictal-onset tachycardia has been recognized in as many as 87% of seizures, not all studies have shown baseline heart rate to be higher in patients with epilepsy, and tachycardia alone appears not to indicate an increased risk for SUDEP. Nor has evidence emerged to link vagal changes in heart rate variability to SUDEP.

In epilepsy, ictal bradycardia of less than 40 beats per minute is less frequent than ictal tachycardia, occurring in 2% to 13% of patients. A number of case reports of SUDEP have described ictal bradycardia and sinus arrest, for which reason ictal asystole has been postulated as a SUDEP mechanism. Studies of epilepsy patients undergoing video-EEG monitoring have found the rate of ictal asystole of more than 5 seconds to be 21 to 32 events per 100 person-years of monitoring.

**RESPIRATORY DYSFUNCTION**

Since ictal hypoxemia, which results from central hypoventilation and, to a lesser degree, obstructive or mixed apnea, frequently occurs during seizures, more pronounced or prolonged ictal hypoxemia may be a determining factor in some cases of SUDEP. Reports of SUDEP have described central apnea, airway obstruction from prone positioning or laryngeal constriction, and pulmonary edema.

Concomitant suppression of respiratory drive and ictal asystole during SUDEP may conduce one another. For example, seizures that are associated with oxygen desaturation increase the likelihood of QTc prolongation by 4.3-fold as compared to seizures that do not impair oxygen saturation. In other cases respiratory suppression, ictal asystole, and dysregulations of systemic or cerebral circulation may arise from a common ictal disturbance of central autonomic regulation.

**AUTONOMIC FACTORS**

Seizure networks may involve any of a number of extensively interconnected central nervous system structures that regulate cardiovascular autonomic outflow. These consist of the insula, the medial prefrontal cortex, the hypothalamus, the hippocampus, and the amygdala, all of which relay neural activity to autonomic centers in the brain stem, including the nucleus tractus solitarius, the ventrolateral medulla, the periaqueductal gray, the nucleus ambiguus, and others. Through central connections with these structures, ictal discharges can potentially influence or impair cardiorespiratory functions.

One mechanism by which autonomic disruption might promote cardiac arrest is by ictal sympathovagal imbalance. It is well established that sympathetic hyperactivity is arrhythmogenic, whereas vagally mediated heart rate variability exerts a protective influence. ECG spectral analysis has found that ictal heart rate variability is decreased. Noting that SUDEP occurs preferentially during sleep, and heart rate variability decreases during sleep, SUDEP might result from a sudden increase in catecholamine release during nocturnal seizures or awakenings while in a state of reduced vagal tone. Extrapolating from these findings, it is possible that ictal suppression of cardiovagal activity might predispose to SUDEP, although at this time no direct evidence exists.

In other cases of SUDEP, there have been reports of increased vagal tone leading to bradycardia or asystole, analogous to vasovagal syncope, or postictal hypotension analogous to vasodepressor syncope, which are benign conditions that, apart from epilepsy, are almost never fatal. The report of a case of ictal syncope-associated transient third degree atrioventricular conduction block in a patient with a lesion in the left insula further strengthens the theory that peri-
ictal disruption of the central autonomic network may underlie SUDEP.46

GENETIC FACTORS

Now that the human genome has been sequenced, ensuing genetic discoveries promise to lead to individualized medical therapy. Ultimately, genotyping may afford patients the opportunity for a patient-specific diagnosis and treatment. In regard to SUDEP, a number of clinical phenotypes of risk have been identified, but measurable specific genetic biomarkers that would allow reliable prediction or affect treatment choices are a very desirable goal.

Genetic factors may play an important role in SUDEP. The pathophysiology underlying SUDEP likely implicates single and combination genetic dysfunctions involving the cerebral, cardiovascular, and respiratory systems. For example, several genes linked to epilepsy have also been tied to inherited cardiac arrhythmias. This association suggests a common genetic link between the molecular basis of epilepsy and some forms of cardio- genic death. These neurocardiac channelopathy genotypes have implications for the phenotypic expression of SUDEP. Genes that have a primary expression in the nervous system yet influence the heart via the autonomic nervous system may result in neurocardiac dysfunction, especially when polymorphisms are encountered.

SCN1A is a gene that encodes the alpha subunit of brain-type tetrodotoxin-sensitive voltage-gated Nav1.1 sodium channels and is highly expressed in the brain (with low-level expression in the heart). The Nav1.1 channels have their highest concentration in neurons of the hippocampus, thalamus, cerebellum, and brainstem, all of which are areas of importance for generating and terminating seizures in humans. SCN1A-associated sodium channelopathies have been associated with severe myoclonic epilepsy of infancy (Dravet syndrome) and generalized epilepsy with febrile seizures plus (GEFS+), which are 2 severe forms of human epilepsy. SCN1A variants are of particular relevance to SUDEP since both Dravet syndrome and GEFS+ have been linked anecdotally to SUDEP.61,62 Dravet syndrome is associated with a high mortality rate, exhibiting reduced heart rate variability and greater QT dispersion in the ECG. These findings are relevant to SUDEP as they reflect amplification of normal sympathetic tone that could stress the cardiovascular system.62 Other gene mutations of the sodium channels have been implicated in human pedigrees, albeit less frequently (eg, SCN8A).

A potassium channelopathy might confer increased risk for SUDEP in humans. The KCNA1 gene has been linked to brain-driven cardiac dysfunction in a mouse model of SUDEP and to epilepsy in humans. In rodent models, KCNA1 gene deletion results in severe generalized motor seizures that culminate in death in about 75% of animals by the age of 10 weeks.63 In humans, KCNA1 gene mutations are predominantly associated with a movement disorder (episodic ataxia type 1) through inherited missense mutations and have also been associated with epilepsy in at least 3 families.64 HCN2 is one of a 4-member family of genes encoding a hyperpolarization-activated, cyclic nucleotide-gated cation channel passing a mixed Na+-K+ inward current, and becoming active with hyperpolarization at less than –50 mV.65 In humans, screening of HCN1 and HCN2 genes in patients with epilepsy has identified a recessive missense mutation resulting in a loss of function of the channel gating region of HCN2 to increase neuronal excitability in genetic generalized epilepsy.66 In a postmortem analysis of 48 SUDEP cases, 2 different nonsynonymous changes in
HCN2 (F738C and P802S) were found to be associated with SUDEP, suggesting that HCN2 variants may underlie susceptibility to sudden death. A recently discovered link between PRRT2 and benign familial infantile epilepsy led to the report of a 14-year-old boy with epilepsy who experienced probable SUDEP. The PRRT2 is a gene that encodes a protein of unknown function and is not an ion channel that is typically associated with epilepsy.

Another set of gene mutations that could impact cardiac function include those affecting the cardiac genes. Among the most promising candidate genes that are being identified as potential SUDEP biomarkers are genetic variants in the long QT syndrome. The long QT syndrome is coupled with mutations in 12 different cardiac genes that code for ion channels or channel-associated proteins. Of the 12 genetic subtypes, the vast majority of cases are caused by mutations in the KCNQ1 gene (LQT1), followed by KCNH2 (LQT2), and SCN5A (LQT3). Mutations in the RYR2 cardiac gene have also been linked to SUDEP in humans. The above genes that are associated with SUDEP are predominately expressed in the heart but are also expressed variably in the brain. In addition, neurorespiratory genes associated with SUDEP have been described.

The search for genomic biomarkers that may be predictive of SUDEP is in its infancy, with many candidate genes that reflect the heterogeneity of the epilepsies. The principal genes studied in SUDEP autopsy cases have included SCN1A, LQT5, KCNQ1, KCNH2, and SCN5A. The potential for invasive monitoring (ie, implantable loop devices) or even implantable defibrillators according to cardiac gene risk profiles may eventually prove useful in preventing SUDEP. Discovering genetic variations and understanding mechanisms in epilepsy represent the first steps toward obtaining a biomarker for SUDEP that may ultimately impart the opportunity to intervene and eliminate SUDEP, which comes upon young individuals and their families as a horrific surprise.

**ANTIEPILEPTIC DRUGS**

Seizures have been shown to cause various changes in cardiorespiratory function. These may consist of tachycardia, bradycardia, serious arrhythmias including asystole, as well as tachypnea, hypopnea, transient respiratory arrest, and hypoxemia. ASDs provide seizure freedom in the majority of patients. However, incomplete seizure freedom occurs in two-thirds of patients with focal seizures and infrequently in patients with encephalopathic generalized epilepsies.

Drug resistance is a risk factor for SUDEP. The risk of SUDEP appears to be even higher in untreated patients. Similarly, those who comply poorly with ASD therapy have similar risks for breakthrough seizures. Subtherapeutic drug levels are not uncommon in patients who experience SUDEP. For patients with genetic generalized epilepsies, the use of a narrow-spectrum ASD may result in a pseudo-drug resistance that is important to recognize. Video-EEG monitoring has been critical in classifying patients for optimal ASD treatment. The incorrect choice of an ASD may be remediable when a switch to broad spectrum agents is made. Therefore, ensuring that drug-resistant patients are properly identified for the proper ASD treatment as well as identifying surgical candidates are important. Monotherapy in one study was found to be protective. Additional ASDs beyond a single agent were found to confer no greater risk reduction beyond that achieved by reducing seizure frequency. Clinical trials evaluating adjunctive ASD therapy for patients with drug-
resistant epilepsy were reviewed by Ryvlin et al, who performed a meta-analysis of more than 100 placebo-controlled studies and found that in the active drug treatment cohort, the risk of SUDEP was nearly sevenfold less than in their counterparts involved in the placebo arms.74

A number of studies have found specific ASDs to be related to SUDEP. Carbamazepine use, toxic doses, and rapid fluctuation in serum concentrations have correlated with SUDEP.16,75 Lamotrigine has also been implicated with SUDEP in patients with generalized seizures.76 Furthermore, lamotrigine is frequently used in women with epilepsy who are planning pregnancy. An estimated 1 in 1000 women with epilepsy die from epilepsy (mostly SUDEP) during or shortly after pregnancy.77 Fluctuation of serum ASD concentrations may contribute to this risk. Physicians should, therefore, be proactive in maintaining therapeutic lamotrigine levels during pregnancy. In contrast, the majority of reports have not found an association between a specific ASD and SUDEP.78 However, some less frequently utilized ASDs may confer an indirect risk for cardiac rhythm alteration.26 Therefore, a 12-lead ECG is recommended prior to beginning ASDs that may result in prolongation of the QTc interval (ie, rufinamide or ezogabine), while some recommend ECG for screening purposes in all patients with uncontrolled epilepsy.

Withdrawal of ASDs raises the risk of GTCs and potentially the risk for SUDEP. To date, no controlled data are available regarding the risk-benefit ratio of withdrawing ASDs when patients are admitted for video-EEG monitoring. Most patients admitted for video-EEG monitoring will require ASD reduction to achieve the goal of recording seizures. Twenty-four-hour uninterrupted supervision, especially at night, and timely attendance after a GTC are paramount to provide optimal patient safety and to prevent SUDEP in the epilepsy monitoring unit setting.9

The risk for SUDEP is even higher in patients taking 3 or more ASDs as compared to those on monotherapy.17 Although ASD polytherapy has been reported to be a strong risk factor for SUDEP, it appears primarily to reflect uncontrolled epilepsy. More recent analysis of 216 cases and 831 controls with epilepsy found that, after controlling for multiple confounding factors such as seizure frequency, the number and type of ASDs were not independently associated with an increased risk for SUDEP.79

### PREVENTION

The development of an effective strategy to overcome SUDEP (Table 2) would be advanced by a greater understanding of pathophysiology and identification of risk factors. Unfortunately the pathogenesis remains incompletely known. Respiratory and cardiac dysfunctions clearly occur, but the precise underlying mechanisms remain elusive. SUDEP is a highly unpredictable and seemingly random event, and there is no proven absolutely effective preventive intervention, although patients with near-SUDEP have been successfully resuscitated when caught in time. Whereas witnessed cases of definite SUDEP are limited, SUDEP has been associated with a seizure occurring prior to the terminal event in 38% to 80% of cases.16,80 Therefore, a rational prevention strategy is seizure remission or elimination with a primary target of minimizing the risk of breakthrough GTCs by providing optimal medical management and patient education.81

Control of all seizures is the therapeutic target with the goal of preventing SUDEP as well as maintaining overall health. However, when sei-
Sudden Unexpected Death in Epilepsy

Knowledge may aid prevention. Providing patients with information about SUDEP is an important approach. In addition to patient education, providing accurate information on SUDEP to medical providers is key to increasing awareness. The spin-off of providing education on SUDEP is that it emphasizes the need for seizure control and helps reinforce patient compliance with ASDs, in addition to limiting risky lifestyles such as sleep deprivation, substance abuse, and poor nutrition. An evidence-based checklist centered upon risk factor modification has been developed to help focus on minimizing individual patient risk factors and promote safety.

Serum ASD concentrations can provide proof of compliance or inadequate dosing when poor seizure control or fluctuating adverse effects are encountered. It is important to keep in mind that inadequate compliance is a common occurrence and one of the modifiable risk factors in epilepsy as well as for SUDEP. Even patients with controlled epilepsy are at risk for SUDEP following a single breakthrough seizure. Drug resistance is defined by 2 or more appropriate ASDs being ineffective in completely controlling seizures at adequate doses over an appropriate period of time. For patients with uncontrolled seizures, ensuring correct classification of the epilepsy syndrome and optimal ASD management might be enhanced by frequent review or re-review of ASD regimens (as in the case of “pseudo-resistance” due to inappropriate ASD selection) when seizures remain uncontrolled.

Furthermore, earlier referral for neurosurgical intervention may help avert the risk for SUDEP, given that epidemiological evidence has shown that successful epilepsy surgery and the recent addition of an ASD are protective. Discussing SUDEP with patients when addressing the immediate risk of epilepsy surgery adds perspective to the patient’s understanding of the potential for risk from uncontrolled seizures. Reports from epilepsy centers have shown that successful epilepsy surgery results in a lower risk of SUDEP compared with those

### Table 2. Current Strategies to Minimize the Risk of SUDEP

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
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<tbody>
<tr>
<td>Provide educational information on SUDEP to epilepsy patients and their families</td>
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<tr>
<td>Ensure an appropriate and adequate dose of ASD with optimal serum concentrations</td>
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<tr>
<td>Ensure patient compliance</td>
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<tr>
<td>Advocate for behavioral modification when needed (substance use and abuse, irregular sleeping habits)</td>
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<tr>
<td>Use ASD monotherapy when possible and advise caution during ASD transition</td>
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<tr>
<td>Avoid QT-prolonging drugs if the ECG shows a baseline prolonged QT interval</td>
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<tr>
<td>Advise regular medical evaluations (especially with a pertinent personal or family history)</td>
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<tr>
<td>Recommend video-EEG monitoring when seizures are drug-resistant to ensure diagnosis and classification are correct</td>
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<tr>
<td>Recommend an epilepsy surgery evaluation when focal seizures are drug-resistant</td>
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<tr>
<td>Suggest developing a process for overnight monitoring when sleep is unattended</td>
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ASD = antiseizure drug; ECG = electrocardiogram; EEG = electroencephalography.
who experience ongoing seizures. However, only 30% to 50% of epilepsy patients are candidates for epilepsy surgery. Weighing the individual risk for SUDEP is another important approach to prevention if seizure control cannot be obtained.

Another potential means of prevention involves intervention to reduce the risk of GTC-induced postictal respiratory compromise. The impact of sleep position on the risk of SUDEP (as in sudden infant death syndrome) emphasizes a role for interventions that prevent the prone position. A seizure ending in the prone position, face-down into a pillow, could obstruct the airway and lead to respiratory compromise. In one study, 71% of SUDEP patients were found in the prone position at a frequency greater than predicted by chance alone. In postictal coma, patients are unable to correct their positioning and are more vulnerable to respiratory insufficiency as well as variable degrees of suffocation. Night-time supervision has been shown to be protective against SUDEP. Dedicated uniform safety measures during epilepsy monitoring where ASDs are withdrawn could be improved by guidelines ensuring multimodal monitoring of essential vital signs as well as ensuring the ready availability of rapid response teams and nursing assistance to prevent peri-ictal cardiorespiratory distress. Supplemental oxygen applied following a seizure may be useful in humans, although evidence thus far has been limited to animal models.

Pharmacotherapy, including drugs utilizing a serotonergic pathway, might offset the risks of SUDEP by reducing the postictal risk of respiratory insufficiency from central apnea. Rodent models of SUDEP as well as research in a presumably related condition, sudden infant death syndrome, have implicated abnormalities of brainstem serotonin transmission. Extrapolating from these models, future strategies to prevent SUDEP may find benefit from selective serotonin reuptake inhibitors (SSRIs), although this hypothesis requires testing through clinical trials. Another potential pharmacotherapeutic approach could involve opioid or adenosine receptor inhibitors. These are potential mechanisms that have theoretical potential to reduce the severity of the postictal state. In addition, the development of information systems and automated devices are advancing, and these technologies may create better means of detecting seizures and providing night-time supervision.

FUTURE DIRECTIONS

Future directions into SUDEP research have explored new avenues, some of which involve novel technology and were discussed at a workshop sponsored by the National Institutes of Neurological Disorders and Stroke in 2008. To further investigate the 2000 cases of SUDEP identified every year in the United states, centralization of information, postmortem standards and selected tissue analysis at autopsy, and development of a registry and central tissue bank were suggested, in addition to responding to other risk factors (Table 3).

Several devices are emerging or are in development to detect seizure activity and relay the information to others who may be able to intervene or resuscitate SUDEP during the crucial moments when death may be preventable. Some of these devices are designed to detect ictal asystole, ictal bradycardia, or other cardiac rhythm changes provoked by abnormal neural activity during a seizure that disrupts central autonomic regulatory centers in the brain. Such changes are potential harbingers of SUDEP. Implantable loop devices are capable of performing prolonged ECG monitoring in high-risk suspects. Implantable permanent
programmable pacemakers and defibrillators may be considered for patients proven to have ictal bradycardia and asystole. Developing comparable systems for preventing SUDEP is potentially a future approach for epilepsy patients.81

Devices currently in existence are primarily aimed at detecting convulsions to alert family or caregivers of an event. The use of a “baby monitor” with auditory capability to hear a seizure has been employed by families of patients with epilepsy. Seizure detection systems are emerging that may have principal application during sleep when the risk for unattended seizure patients is greatest. Non-EEG monitors are being developed to detect abnormal motions (accelerometers) created by a seizure, or to detect ictal tachycardia (ambulatory ECG). These techniques are more widely available and more practically applied to the body than EEG. Potentially, these devices can help reduce the risk of mortality by warning of ongoing convulsions, identifying patients at risk for SUDEP, and assisting with resuscitation in patients with SUDEP. Limited evaluation has been performed thus far, and more devices are currently in development. Most commercially available systems do not employ EEG and will realize their full potential for accuracy in the future.

Accelerometers that sense the rapid muscular contractions during seizures are beginning to use Bluetooth technology and management software to couple detection, transmission, and alerting capabilities. SmartWatch® is an example of a wrist-worn device incorporating an accelerometer that detects the rhythmic repetitive movements during a seizure. The device sends a signal via a wireless link to a self-designated computer, smartphone, or other device to alert family or caretakers of an episode requiring prompt intervention. The information is stored in the form of a digital event, Table 3. Patient Risk and Future Approaches to Identification and Treatment

<table>
<thead>
<tr>
<th>Risk</th>
<th>Approach</th>
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<tbody>
<tr>
<td><strong>General</strong></td>
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<tr>
<td>High risk</td>
<td>Address personal and family history of sudden death, fetal demise, environ-</td>
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<tr>
<td>mental risks, sleep habits, and drug use</td>
<td></td>
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<tr>
<td>High risk</td>
<td>Chronic ambulatory multimodal device monitoring of EEG with ECG and oxygen measurement</td>
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<tr>
<td>All epilepsy patients</td>
<td>Serial phone calls, reminders, calendars, or questionnaires to track information about medications, illicit drug use, alcohol consumption, ASD compliance, regular sleeping habits, and SUDEP awareness</td>
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<tr>
<td><strong>Cardiac</strong></td>
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<tr>
<td>Personal or family history of heart disease</td>
<td>Obtain 12-lead ECG to assess the potential for electrophysiologic cardiac dysfunction</td>
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<tr>
<td>Ictal bradycardia or asystole</td>
<td>Cardiac evaluation for implantable cardiac pacemaker or pacemaker-defibrillator</td>
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<tr>
<td>Epilepsy monitoring</td>
<td>Multimodal EEG, ECG-cardiac, and respiratory monitoring (especially if undergoing ASD taper and overnight recording)</td>
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<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
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<tr>
<td>GTC seizures</td>
<td>Measure baseline and peri-ictal oxygen saturation</td>
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<tr>
<td>Nocturnal seizures</td>
<td>Consider overnight polysomnography with attention to the degree of hypopnea/apnea, sleep efficiency, and arousability</td>
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<tr>
<td>Respiratory failure</td>
<td>Pulmonary evaluation for diaphragmatic pacing</td>
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<tr>
<td><strong>Autonomic</strong></td>
<td></td>
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<tr>
<td>Ictal symptoms with autonomic features</td>
<td>Autonomic evaluation including heart rate variability, baroreceptor sensitivity, and response to Valsalva</td>
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<tr>
<td><strong>Blood</strong></td>
<td></td>
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<tr>
<td>High risk patients</td>
<td>Blood banking for genomic analysis, C-reactive protein, postictal troponin, and postictal brain natriuretic peptide</td>
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with the corresponding time and date, duration, and motion analysis, which are then trended in graphic format (http://www.smart-monitor.com/for-clinicians/). The device was able to detect 90% of 39 convulsive seizures in 20 patients (age 6 to 68 years) admitted to an epilepsy monitoring unit and had a false detection rate of 0.2/day. In a study that compared video-EEG monitoring with accelerometers to detect nocturnal hypermotor seizures in children, accelerometers had a sensitivity of 96% and a positive predictive value of 58%. Combined techniques measuring skin resistance, temperature, and movement using an accelerometer with electrodes sensing electrodermal activity have shown improved detection over accelerometers alone, detecting 15 of 16 GMS in 7 patients, with 0.74 false alarms per day. The design allows motion detection to signal others that a seizure is in progress. Limitations include false-positive detections that identify nonictal movement.

Emerging dual technologies with electrodermal activity may improve upon the number of true positive detections. Another device (SMART Belt®) is a seizure-monitoring belt worn around the upper chest that has a multi-sensor design to continuously measure patient respiration and electrodermal activity. It synchronizes the changes in both to alert caregivers at the onset of a seizure by detecting increased electrical conductance in the skin and the alterations in rate of respiration. The device costs approximately $100 to produce and is designed for seizure detection in the outpatient setting (http://aac-rerc.psu.edu/wordpressmu/RESNA-SDC/2013/06/13/smart-belt-a-low-cost-seizure-detection-device-rice-university/).

There are still other devices geared toward sleep. Anti-suffocation pillows and methods of indirectly sensing vibration, such as mattress-based designs, appear to have more limited specificity, with numerous false-positive detections. Whether non-EEG devices will ultimately enable meaningful postictal intervention to prevent SUDEP remains to be determined. In the future, if reliable biomarkers to reflect high-risk patient profiles can be identified, mortal cardiac failure might be preventable through implantation of cardiac pacemaker-defibrillators.

CONCLUSION

SUDEP warrants vigilant clinical attention because it is the leading cause of nontraumatic epilepsy-related death, especially among young adult males and patients with frequent seizures, nocturnal seizures, symptomatic etiologies, and drug-resistant seizures not well-controlled by medication. Efforts to identify which patients are at greatest risk, to elucidate the pathophysiology, and to identify predictive biomarkers are paramount to prevention. Considerable progress has been made thus far, but there is much more still to do.

REFERENCES


68. Labate A, Tarantino P, Palmara G, et al. Mutations in PRRT2 result in familial infantile seizures with heteroge-


