Sudden unexpected death in epilepsy

AUTHORS: Steven C Schachter, MD, Joseph I Sirven, MD
SECTION EDITOR: Paul Andrew Garcia, MD
DEPUTY EDITOR: John F Dashe, MD, PhD

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INTRODUCTION

Patients with epilepsy have a small risk of sudden unexpected death, a condition referred to as sudden unexpected death in epilepsy (SUDEP) [1,2]. SUDEP is defined specifically as the sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicologic cause for death [3].

The cause of SUDEP is uncertain. Observations in individual cases have suggested possible cardiogenic, pulmonary, and primary neurologic etiologies. It may be that SUDEP is a heterogeneous condition. The vast majority of witnessed cases have been associated with a seizure, and the main risk factor is uncontrolled seizures, especially generalized tonic-clonic seizures.

This topic discusses risk factors, causes, and prevention strategies for SUDEP. The management and other complications of seizures and epilepsy are discussed separately. (See "Overview of the management of epilepsy in adults" and "Evaluation and management of drug-resistant epilepsy".)

DEFINITION

Sudden unexpected death in epilepsy (SUDEP) is defined specifically as the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus ≥30 minutes in

duration, in which postmortem examination does not reveal a structural or toxicologic cause for death [3,4].

The category of possible SUDEP includes cases that otherwise meet criteria for SUDEP but have competing causes of death [3]. Near SUDEP describes cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than one hour.

INCIDENCE

Sudden unexpected death in epilepsy (SUDEP) causes between 2 and 18 percent of all deaths in patients with epilepsy [5-9]. This proportion may be somewhat higher in children [10,11].

A 2017 systematic review and meta-analysis by the American Academy of Neurology (AAN) identified 12 studies on the incidence of SUDEP of low to moderate quality [12]. Based on these studies, the overall incidence of SUDEP was estimated at 0.58 per 1000 person-years (95% CI 0.31-1.08). The incidence was lower in children (0.22 per 1000 person-years, 95% 0.16-0.31) and higher in adults (1.2 per 1000 person-years, 95% CI 0.64-2.32).

Some but not all reports published after the AAN meta-analysis suggest that the incidence of SUDEP in children is similar to the incidence in adults [11,13]. As an example, a Swedish population-based study that included more than 57,000 people with epilepsy found a higher overall incidence (1.2 per 1000 person-years) and a higher incidence in children (1.11 per 1000 person-years) than previously reported [11]. However, a population-based report from Denmark found a lower risk of SUDEP in children compared with adults [14]. The authors of the Swedish study noted that only two-thirds of probable and possible SUDEP cases had epilepsy listed on the death certificate, suggesting that studies using death certificates for case ascertainment may underestimate incidence [11]. A separate study from the San Francisco area came to similar conclusions [15].

The incidence of SUDEP increases with severity of epilepsy, and may be as high as 0.5 to 1 percent a year in those with severe refractory epilepsy [1,5]. In adult epilepsy monitoring units, the incidence of SUDEP has been estimated at 5 per 1000 epilepsy patient-years, with a risk of 1.2 cases per 10,000 video electroencephalogram (EEG) monitoring studies [16].

The lifetime cumulative risk for SUDEP by age 40 has been estimated at 7 percent overall, or 12 percent in those with persistent epilepsy [10]. The cumulative full lifetime risk has been estimated to be 35 percent [17].

RISK FACTORS

Seizure type and frequency — The most important risk factor for sudden unexpected death in epilepsy (SUDEP) is the presence and frequency of generalized tonic-clonic seizures [12,18]. Patients with generalized tonic-clonic seizures have a 10-fold higher risk of SUDEP compared with those who do not have generalized tonic-clonic seizures, and those with three or more generalized tonic-clonic seizures per year have a 15-fold increased risk of SUDEP compared with those who have fewer than three per year. This translates to an absolute risk of up to 18 deaths per 1000 person-years in patients with frequent generalized tonic-clonic seizures.

Convulsive seizures have also been associated with unexplained sleep-related deaths in children without previously recognized seizures. A registry of 301 children with unexplained sudden death included seven children (age 13 to 27 months) with home video recordings of their last sleep period [19]. Six of the seven children had a terminal event consistent with a convulsive seizure.

Age — Most reported cases of SUDEP are in young adults between the ages of 18 and 40 years, but children younger than one year can be affected [6,8,20-22]. The incidence of SUDEP may be up to five times higher in adults compared with children [12]. (See 'Incidence' above.)

SUDEP is relatively unusual in individuals greater than 45 years. However, the latter observation may be due to under-reporting of sudden death as SUDEP in an older individual, particularly if there are medical comorbidities.

Genetic factors — A genetic predisposition to SUDEP has long been entertained based on the observation that genetic mutations in ion channels underlie some forms of epilepsy as well as syndromes associated with cardiac arrhythmias and sudden death, such as the congenital long QT syndrome (LQTS) [23].

Some cases of SUDEP may in fact be caused by LQTS. This was suggested by a study of 61 SUDEP cases for which whole blood was collected at autopsy and later analyzed by exome sequencing [24]. Pathogenic mutations in LQTS genes were identified in four patients (7 percent), and an additional nine patients (15 percent) had candidate pathogenic variants in dominant cardiac arrhythmia genes. None of the SUDEP cases had a history of cardiac disease. Electrocardiograms (ECG) were available in six of the patients with pathogenic or candidate LQTS variants; all showed normal sinus rhythm, five had a normal corrected QT interval, and one had a borderline corrected QT. These findings need to be confirmed in other studies and validated prospectively to determine whether there is a role for genetic testing in epilepsy

patients. Review of a routine ECG is important in the initial evaluation of all patients with epilepsy. (See 'Counseling and prevention' below.)

This study also found a relatively high frequency of *DEPDC5* mutations in SUDEP cases, although this may merely reflect that *DEPDC5* is a common cause of focal epilepsy [24]. (See "Focal epilepsy: Causes and clinical features", section on 'Genetic focal epilepsy syndromes'.)

Mutations in sodium channel genes (eg, *SCN1A*, *SCN1B*, *SCN2A*) were identified in several patients with epileptic encephalopathy [24]. Other studies have also suggested that patients with Dravet syndrome (DS), caused in many cases by *SCN1A* mutations, may have cardiac alterations that put them at increased risk for SUDEP [25]. (See "Dravet syndrome: Genetics, clinical features, and diagnosis".)

Other clinical and demographic features — Observational evidence supports the following additional risk factors, many of which may be markers of poor seizure control or epilepsy severity [12,18,26-28]:

- Lack of nighttime supervision (eg, living alone or not sharing a bedroom)
- Not being seizure-free for one to five years
- Not adding an antiseizure medication when patients are medically refractory
- Nocturnal seizures
- Total number of antiseizure medications used
- Never having been treated with an antiseizure medication
- Antiseizure medication nonadherence
- Extratemporal epilepsy
- Intellectual disability
- Male sex
- Lamotrigine use in women
- Anxiolytic drug use

Other clinical and demographic features with very low quality or conflicting evidence to support an association with SUDEP risk include [2,5,8,12,16,26,29-34]:

- Overall seizure frequency when evaluated by using all seizure types
- Medical refractory epilepsy, independent of seizure control in the last year
- Subtherapeutic antiseizure medication levels
- Polytherapy versus monotherapy
- Psychotropic drug use
- Alcoholism
- Long duration of epilepsy

- Younger age of onset of epilepsy
- Idiopathic versus localization-related epilepsy
- Structural lesion on neuroimaging
- Resective epilepsy surgery (associated with reduced risk)
- Use of vagus nerve stimulator (associated with reduced risk)

One systematic review of selected cases reports and case series identified prone sleep position as a possible risk factor for SUDEP [35]. This was based on the finding that prone positioning at the time of death was reported in 73 percent of SUDEP cases (n = 253) in which body position was adequately documented. However, only a small number of published SUDEP studies were included in the analysis (25 out of 1106), since most articles did not include information about sleep positioning. A subsequent population-based report from Sweden noted that a prone position was present in 70 percent of all SUDEP cases with documented body position (n = 143), and in 80 percent of those who died at night (n = 190) [36]. Additional studies are needed to understand whether sleep position might be a modifiable risk factor for SUDEP, as is the case in sudden infant death syndrome.

PATHOPHYSIOLOGY

While sudden unexpected death in epilepsy (SUDEP) is only rarely witnessed, most observations suggest that SUDEP usually occurs in the context of a seizure [2,4,22,37]. Cases of witnessed sudden cardiac arrest meeting criteria for SUDEP and without a preceding seizure have been described, however, including several cases in which electroencephalogram (EEG) excluded subclinical seizure activity [38,39]. Many SUDEP deaths occur at night while the patient is asleep in bed [4,8,20,22,40].

No singular mechanism has been established, and multiple pathophysiologic factors may be involved, including cardiac arrhythmia, seizure-induced respiratory changes and pulmonary dysfunction, and neurogenic cardiorespiratory depression [2,8,26,37,41-49]. Genetic factors may also play a role in predisposing patients to SUDEP. (See 'Genetic factors' above.)

Cardiogenic factors — Indirect evidence suggests that cardiogenic mechanisms, including cardiac arrhythmias and cardiovascular disease, may be involved in some cases of SUDEP. In one prospective population-based cohort study of more than 2000 cases of sudden cardiac arrest, 4.4 percent of patients had a history of epilepsy and among these patients, two-thirds of witnessed arrests were not preceded by clinical seizure activity [39].

Although the pathophysiology is uncertain, there is evidence suggesting that epilepsy leads to acquired cardiac ion channel dysregulation, perhaps via cortical autonomic dysfunction and structural cardiac disease [50,51]. In turn, an acquired cardiac channelopathy may lead to an increased risk of malignant arrhythmias and sudden death.

Ictal bradycardia and asystole — Ictal bradycardia, atrioventricular block, and even asystole can be observed in some patients with epilepsy [52-57], raising the possibility that some cases of SUDEP are explained by this phenomenon. However, the relationship between ictal heart rate changes and SUDEP is not firmly established, and it is not known whether patients with ictal bradycardia or asystole have an increased risk of SUDEP compared with those who do not have these features.

The frequency of bradycardia and asystole in patients with epilepsy is uncertain [58]. In one series that reviewed long-term EEG monitoring data on 1277 seizures in 69 patients with drug-resistant epilepsy, rates of ictal bradycardia and asystole were 7 and 2.9 percent [55]; in a series of 6825 patients on long-term monitoring, the rate of ictal asystole was only 0.15 percent [53]. Although classically considered to be associated with left temporal seizures in patients with longstanding epilepsy, ictal asystole can also occur early in the course of epilepsy and can be caused by right temporal as well as frontal and insular seizures [57].

Both ictal bradycardia and asystole are unusual in children. In one case series of 49 children who had seizures on a monitoring study, ictal bradycardia occurred in 3.7 percent of seizures and only during partial complex seizures of extratemporal onset [59].

Monitoring studies have identified clinical features that suggest an ictal arrhythmia. Diffuse atonia has been observed to accompany episodes of asystole lasting longer than eight seconds [53,54]. In three patients with focal epilepsy, sudden falls occurred due to seizure-induced asystole [60]. These observations suggest that when seizures include a delayed loss of tone, clinicians should consider the possibility of ictal asystole and need for cardiac monitoring. The recurrence risk of ictal asystole may be as high as 30 to 40 percent [61]. Pacemaker implantation appears to reduce falls and secondary morbidity in patients with seizure-induced asystole and bradycardia when seizures are not controlled by other therapies [62,63].

At least one investigation observed that the cardiovascular characteristics of ictal asystole were similar to tilt-table induced vasovagal asystole [64]. The authors speculated that ictal asystole might share a pathophysiologic mechanism with vasovagal syncope and perhaps be similarly benign.

Prolonged QT interval and tachyarrhythmias — Seizure-induced changes in the QT interval or autonomic instability, predisposing to malignant arrhythmias, have also been proposed as

possible mechanisms in SUDEP. Support for this mechanism is bolstered by the finding that some patients with SUDEP carry a pathogenic mutation in one of the genes associated with congenital long QT syndrome (LQTS). (See 'Genetic factors' above.)

Seizure-induced changes in the QT interval have been described, although their significance is not clear. A number of case series of combined EEG-electrocardiogram (ECG) telemetry have noted prolongation of the QT interval during seizures in 12 to 23 percent of patients [65-69]. This finding may be associated with potentially fatal ventricular arrhythmias. However, in a matched case-control study, a prolonged QT interval was not specifically associated with SUDEP [67].

A pre-ictal shortened QT interval has also been observed but is of uncertain clinical significance [68]. Other ECG markers for cardiovascular arrhythmia and mortality (T-wave alternans, ventricular late potentials) have also been found to be more prevalent in patients with epilepsy compared with controls in small case series [70,71].

Direct evidence of mortality from seizure-induced cardiac arrhythmias is lacking [58], and the etiologic link between seizures and cardiac arrhythmias and possibly sudden cardiac death remains to be established [72,73]. In one study of 21 patients with SUDEP, a prior EEG-ECG recording had revealed ictal cardiac repolarization and rhythm abnormalities in 56 percent of SUDEP patients compared with 39 percent of controls [74]. SUDEP patients also had higher ictal heart rate elevations, particularly in seizures that arose from sleep. However, these data do not indicate that routine ECG recording or ambulatory ECG monitoring can identify which epilepsy patients are at increased risk for SUDEP.

Some authors have suggested that release of catecholamines during seizures may lead to cumulative cardiac injury (takotsubo cardiomyopathy) and possibly a susceptibility to arrhythmia or sudden hemodynamic compromise and cardiogenic shock [75].

The influence of antiseizure medication treatment on SUDEP is another potential factor. Both carbamazepine and phenytoin have been implicated as possibly exacerbating some of the autonomic and cardiac effects of seizures, but an increased risk of either ictal arrhythmias or SUDEP with these or other antiseizure medications has not been demonstrated [58]. Lamotrigine has been identified in some reports as increasing the risk of SUDEP in women with primary generalized epilepsy, possibly through a proarrhythmic effect [30,76]. Other studies, however, were not able to confirm this association [30,77].

Cardiovascular disease — Epilepsy has also been linked to cardiovascular disease, which may predispose patients to sudden cardiac death. A case-control study in Stockholm found that a history of epilepsy was a risk factor for acute myocardial infarction (MI) (odds ratio [OR] = 4.8)

and was associated with a poor prognosis after MI [78]. Other studies have also linked epilepsy and cardiovascular mortality [79,80].

Proposed mechanisms underlying this association between epilepsy and cardiovascular disease include adverse effects of enzyme-inducing antiseizure medications on cholesterol and lipid metabolism and obesity [81]; increased smoking and decreased physical activity in persons with epilepsy [82]; as well as a possible adverse effect of chronic epilepsy upon the heart.

Respiratory dysfunction — Ventilatory failure with ictal hypoxemia and hypercapnia from centrally mediated apnea may underlie some cases of SUDEP; frank apnea is sometimes observed [83-86].

- In a prospective study with evaluable data for 312 seizures, ictal central apnea occurred in 47 percent of patients with focal epilepsy (n = 109), and in 37 percent of partial seizures, but not in patients with primary generalized epilepsy (n = 17) [86]. Oxygen saturation data, available for 79 seizures with ictal central apnea, revealed ictal hypoxemia in 71 percent. Oxygen desaturation considered mild (90 to 94 percent), moderate (75 to 89 percent), or severe (<75 percent) was present in 46, 39, and 14 percent of hypoxemic episodes, respectively. Apnea of 60 seconds or longer was associated with severe hypoxemia. Ictal central apnea was associated with temporal lobe epilepsy compared with extratemporal epilepsy.

- In a series of 56 patients with intractable epilepsy, oxygen saturation dropped below 90 percent in 33 percent of both focal and secondarily generalized seizures, below 80 percent in 10 percent of seizures, and below 70 percent in 3.6 percent of seizures [85]. Seizure duration and temporal lobe localization were risk factors for desaturation. The timing of the apnea appeared to coincide with contralateral spread [87]. Most apnea episodes appeared to be of central origin; 9 percent appeared obstructive. Two patients have been described with seizures whose sole or major ictal manifestation was apnea [83]. In children, the prevalence of ictal hypoxia seems to be similar. In one case series of 225 seizures in 49 monitored children, 27 percent of seizures were associated with ictal hypoxia; in one-third of these, oxygen saturation dropped below 60 percent [59].

- Another case series of 94 recorded seizures in 33 patients revealed elevations in ictal/postictal end-tidal carbon dioxide in 11 patients [88]. Peak end-tidal carbon dioxide was above 50 mmHg in 35 seizures, above 60 mmHg in 15, and above 70 mmHg in 5 seizures. Because the degree of hypercapnia was not associated with apnea or seizure duration, the investigators speculated that it possibly resulted from ventilation-perfusion mismatch or transient pulmonary edema.

These observations do not clearly link apnea to SUDEP; however, in one case, a women undergoing EEG monitoring developed persistent apnea in the setting of a convulsive seizure [45]. Her cardiac rhythm remained intact initially, and she underwent successful cardiopulmonary resuscitation. Another case series found that seizures associated with oxygen desaturation were also more likely to have ictal QT prolongation (OR = 4.3) [69].

Alternative causes of ictal respiratory compromise include laryngospasm, asphyxiation, aspiration, and neurogenic pulmonary edema [72]:

- Laryngospasm was described in a single case of a 40-year-old man who developed stridor and cardiopulmonary arrest during a generalized tonic clonic seizure [46]. He was successfully resuscitated.

- Patients with SUDEP are often found in the prone position [35,36], suggesting that asphyxiation may have played a role in their death [89]. In a few cases of witnessed SUDEP, airway obstruction was evident [37].

- Case series with postmortem examination often find pulmonary edema in patients with SUDEP [20,22,40,41,90]. In one study, the prevalence of this finding was significantly higher in those with SUDEP compared with patients with epilepsy who died of an alternative cause (62 versus 27 percent) [40]. However, the degree of edema observed is typically felt to be insufficiently severe to cause death.

Neurogenic cardiopulmonary dysfunction — Postictal generalized EEG depression has been observed in some cases of monitored SUDEP [91-93]. While the role and pathogenesis of this depression is controversial and may not be causal in all or even most cases, the depth of attenuation may be a marker for the risk of SUDEP.

A pattern of centrally mediated cardiorespiratory collapse has been described based on a multicenter study that included review of 16 SUDEP and 9 near-SUDEP cases occurring in epilepsy monitoring units [16]. Cardiorespiratory and EEG data available from 10 cases showed a consistent and previously unrecognized pattern whereby a triggering secondary generalized tonic-clonic seizure was followed by a short period of normal or increased heart and respiratory rates, after which a combination of central apnea, severe bradycardia, and transient or terminal asystole occurred together with postictal generalized EEG attenuation. These changes typically peaked between one and three minutes after the seizure. The vast majority of these cases occurred at night, which has been previously described as a risk factor for SUDEP and suggests possible circadian differences in the central response to generalized seizures that occur during sleep. The safety implications of these findings for epilepsy monitoring units are discussed

separately. (See "Video and ambulatory EEG monitoring in the diagnosis of seizures and epilepsy", section on 'Safety'.)

Other series of monitored patients without SUDEP have also suggested possible pathogenic roles for a centrally-mediated phenomenon in SUDEP. A retrospective review of video-EEG telemetry studies in 10 patients who subsequently died of SUDEP found that postictal generalized EEG depression was seen in half of these patients compared with 38 percent of seizures in control patients [94]. This period of postictal EEG depression was significantly longer in patients who developed SUDEP. In particular, a duration of >50 seconds was associated with a significantly increased odds of SUDEP. Other factors that have been associated with an increased risk of prolonged postictal generalized EEG depression after a generalized convulsive seizure include longer and more severe periods of postictal oxygen desaturation [95], higher degrees of sympathetic activation and parasympathetic suppression [96], peri-ictal decerebrate or decorticate arm posturing, and lack of early oxygen administration [97,98].

At least one large study was unable to confirm an independent association between postictal generalized EEG depression and SUDEP, finding instead that EEG suppression was simply a marker of secondary generalization [99].

Some have suggested that brainstem adenosine and serotonergic neurotransmitter pathways may be involved in the pathogenesis of SUDEP [48,100]. One hypothesis invokes the inhibition of neuronal activity that modulates respiration in subcortical structures, including the periaqueductal gray, mediated by the release of adenosine during seizures, which leads to respiratory depression [48]. By contrast, serotonin or drugs that enhance the effect of serotonin can enhance respiration. In an animal model of SUDEP in which audiogenic seizures precipitate postictal respiratory arrest, this phenomenon was prevented by administration of a selective serotonin reuptake inhibitor, and induced by the serotonin receptor antagonist, cyproheptadine [101].

COUNSELING AND PREVENTION

Informing patients and caregivers — Informing most or all patients with epilepsy and their caregivers about sudden unexpected death in epilepsy (SUDEP) is strongly recommended; this should be included in the general counseling about the risks of epilepsy and seizures [102,103]. Surveys indicate that a large majority of adult patients with epilepsy and parents of children with epilepsy desire this information [104,105].

Disclosure of SUDEP risk to all patients with a diagnosis of epilepsy as part of a comprehensive education program has been endorsed by multiple societies and consensus groups, including a joint task force of the American Epilepsy Society and the Epilepsy Foundation, a National Institutes of Health multidisciplinary workshop, and the American Academy of Neurology (AAN) [12,72,106]. The AAN has also prepared an informational video that clinicians may find useful as a patient education resource [107].

The potential benefits of counseling as outlined by a panel of experts include [72]:

- Helps clinicians and patients share in treatment goals
- Helps establish "truth-telling relationship"
- Avoids a false sense of security and complacency regarding epilepsy and its treatment
- Allows people with epilepsy to express anxiety about their diagnosis and encourages constructive discussion
- Allows people with epilepsy to organize their lives with reasonable expectations
- Allows people with epilepsy and their caregivers to reduce potential risk factors for SUDEP, promoting compliance and minimizing behaviors that increase seizure risk
- Reduces fear of SUDEP in low-risk populations
- Lessens pain, grief, and blame among families in the event SUDEP does occur

When disclosing SUDEP risk, the AAN practice guideline recommends presenting risk as the probability of both having and not having the event and using numbers in addition to words and frequencies rather than percentages [12]. The AAN believes that presenting information in this way may help to lessen people's tendency to overestimate the risk of an adverse event happening to them.

- For children with epilepsy, parents or guardians should be informed that there is a rare risk of SUDEP. In one year, SUDEP typically affects 1 in 4500 children with epilepsy; in other words, annually, 4499 of 4500 children will not be affected by SUDEP [12].
- Adults should be informed that there is a small risk of SUDEP. In one year, SUDEP typically affects 1 in 1000 adults with epilepsy; in other words, annually, 999 of 1000 adults will not be affected by SUDEP [12].

Strategies to reduce risk — There are no data from clinical trials regarding prevention of SUDEP [108]. Existing strategies come from knowledge of risk factors for SUDEP identified in cohort and case-control studies as well as expert recommendations.

Identify patients at highest risk — Generalized tonic-clonic seizures and poorly controlled epilepsy are major risk factors for SUDEP. (See 'Seizure type and frequency' above.)

Identifying patients at high risk allows the clinician to focus on educating patients and their families and caregivers about SUDEP, ascertaining seizure precipitants, and promoting adherence with treatment [2,109]. Patients should be informed that seizure freedom, particularly freedom from generalized tonic-clonic seizures, is strongly associated with decreased risk of SUDEP.

Optimize treatment of drug-resistant epilepsy — Patients with drug-resistant epilepsy should be referred to a comprehensive epilepsy center for consideration of additional pharmacologic options as well as resective epilepsy surgery, other surgical approaches, and dietary therapies. While these measures have not been proven prospectively to reduce SUDEP risk, the largest risk for SUDEP is uncontrolled generalized tonic-clonic seizures, and it seems reasonable to infer that efforts to improve seizure control may reduce SUDEP risk, among other benefits [12].

- **Surgical therapy** – In one retrospective cohort study, mortality was compared in patients who had epilepsy surgery with those who had presurgical assessment but no surgery [110]. Patients who did not undergo surgery were 2.4 times more likely to die as those who had surgery and were 4.5 times more likely to die a probably epilepsy-related death. Another retrospective, single-center study compared patients who had epilepsy surgery (n = 590) with patients with medically refractory epilepsy who did not have surgery (n = 122); surgery was associated with a lower rate of both all-cause mortality and SUDEP [111]. In a longitudinal follow-up study of patients after temporal lobe resection, the risk for premature death decreased over time, although it remained somewhat higher than the standard population [112]. (See "Surgical treatment of epilepsy in adults".)

- **Pharmacologic therapy** – Treatment with adjunctive antiseizure medications and adherence to therapy are important measures in reducing the risk of SUDEP. In a meta-analysis of placebo-controlled randomized trials in patients with refractory seizures, the risks of definite or probable SUDEP, all SUDEP, and all-cause death were lower when patients who received adjunctive antiseizure medications in efficacious doses were compared with patients in the placebo group during the placebo portion of these trials (odds ratio [OR] 0.17, 0.17, and 0.37, respectively), as determined by seizure outcomes in

at least one randomized trial, not at an individual patient level [113]. Additional support comes from a case-control study that identified 255 cases of SUDEP and 1148 matched living control patients with epilepsy [27]. In adjusted analysis, polytherapy was associated with a reduced risk of SUDEP (OR 0.48, 95% CI 0.26-0.90), while mention of nonadherence in the patient record was associated with an increased risk of SUDEP (OR 2.75, 95% CI 1.58-4.78).

The management of drug-resistant epilepsy is discussed in detail separately. (See "Evaluation and management of drug-resistant epilepsy" and "Seizures and epilepsy in children: Refractory seizures".)

Review routine electrocardiogram — Review of a routine electrocardiogram (ECG) is important in the initial evaluation of all patients with epilepsy. In addition to its role in the diagnostic evaluation of seizure, ECG findings such as a prolonged QT interval may indicate an acquired or genetic predisposition for cardiac arrhythmias and thereby provide the opportunity for anticipatory management and prevention. (See "Evaluation and management of the first seizure in adults", section on 'Electrocardiogram'.)

Serial ECG monitoring has not been evaluated prospectively to determine its impact on managing the risk of SUDEP [58,72,114]. (See 'Genetic factors' above and "Congenital long QT syndrome: Epidemiology and clinical manifestations".)

Nocturnal supervision — Many SUDEP deaths are unwitnessed and occur at night, and postictal respiratory depression appears to be a component of the pathophysiology. These observations raise the possibility that a bedroom observer or monitor could detect seizures, check on the patient, and provide sufficient stimulation to prevent respiratory arrest. (See 'Respiratory dysfunction' above.)

While nocturnal supervision has not been studied in randomized trials, observational data suggest that nocturnal supervision is associated with a reduced risk of SUDEP [115]. As an example, one retrospective case-control study found that supervision at night (defined as the supervising person sharing the same bedroom, or use of special precautions such as regular checks throughout the night, or use of a monitoring device) was associated with a decreased risk of SUDEP (OR 0.4 for supervision and 0.1 for listening device) [116].

Based on these data, it seems reasonable to discuss nocturnal supervision or other nocturnal precautions (such as a remote listening device) as an option in patients with frequent generalized tonic clonic seizures and those who are particularly concerned about the risk of SUDEP. This is consistent with recommendations of an AAN practice guideline on SUDEP

incidence and risk factors [12]. Whether such precautions reduce the risk of SUDEP is not known, however.

Seizure alerting devices — There are a number of devices on the market that serve as seizure alerting devices with the goal of preventing SUDEP [117,118]. These devices alert caregivers or patients based on a number of biomarkers for seizures, ranging from heart rate to muscle contractions and respirations. There are few trials that have shown SUDEP prevention with these devices.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Seizures and epilepsy in adults" and "Society guideline links: Seizures and epilepsy in children".)

SUMMARY AND RECOMMENDATIONS

- Patients with epilepsy have a small but significant risk of sudden unexpected death (SUDEP). The incidence is estimated at 0.2 to 1.1 per 1000 person-years in children with epilepsy and 1.2 per 1000 person-years in adults with epilepsy. (See 'Definition' above and 'Incidence' above.)
- The most significant risk factor for SUDEP is frequent generalized tonic-clonic seizures. (See 'Risk factors' above.)
- The etiology of SUDEP is unknown; most cases appear to occur in the context of a seizure. Multiple pathophysiologic factors may be involved, including cardiac arrhythmia, seizure-induced respiratory changes and pulmonary dysfunction, and neurogenic cardiorespiratory depression. Genetic factors may also play a role. (See 'Pathophysiology' above and 'Genetic factors' above.)
- We recommend that clinicians inform epilepsy patients, family members, and caregivers about the incidence and risk factors for SUDEP. Counseling should include discussion of both the probability of having and of not having SUDEP. (See 'Informing patients and caregivers' above.)
- There are no strategies that have been proven to reduce the risk of SUDEP. Maximizing seizure control is recommended, including medication adherence and timely

consideration of epilepsy surgery for patients with drug-resistant epilepsy. (See 'Identify patients at highest risk' above and 'Optimize treatment of drug-resistant epilepsy' above.)

- Review of a routine electrocardiogram (ECG) is important in the initial evaluation of all patients with epilepsy. In addition to its role in the diagnostic evaluation of seizure, ECG findings such as a prolonged QT interval may indicate an acquired or genetic predisposition for cardiac arrhythmias and thereby provide the opportunity for anticipatory management and prevention. (See 'Review routine electrocardiogram' above.)

- Nocturnal supervision has not been studied prospectively but has been associated with reduced risk of SUDEP in a large case control study. We discuss this information with patients. Although unproven, patients with frequent generalized tonic-clonic seizures or other risk factors may reasonably choose to pursue nocturnal supervision or other precautions. (See 'Nocturnal supervision' above.)

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Contributor Disclosures

Steven C Schachter, MD Patent Holder: Supernus Pharmaceuticals [Epilepsy]. All of the relevant financial relationships listed have been mitigated. **Joseph I Sirven, MD** Consultant/Advisory Boards: Neurelis [Epilepsy]; Neurona [Epilepsy]; UCB [Epilepsy]. All of the relevant financial relationships listed have been mitigated. **Paul Andrew Garcia, MD** Equity Ownership/Stock Options: EnlitenAI Inc [Epilepsy]. Consultant/Advisory Boards: Medtronics [Epilepsy]. All of the relevant financial relationships listed have been mitigated. **John F Dashe, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose.

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