

# Prevention of Sudden Unexpected Death in Epilepsy

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Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death related to epilepsy and is associated with treatment resistance and the presence of generalised tonic-clonic seizures (GTCS, of either focal or generalised onset). While the causative mechanisms of SUDEP are yet to be fully elucidated, it is thought that seizure-induced brainstem suppression, and respiratory and cardiac dysfunction may be involved. Research into SUDEP has identified several risk factors (including frequency of GTCS and male gender) but has also indicated proven or potential preventive strategies, including more effective seizure control. Despite increasing awareness and research into SUDEP, its underlying mechanisms and preventive strategies remain poorly defined. More research is needed into the pathophysiology of SUDEP and to identify predictive biomarkers. Furthermore, clinical trials are warranted to assess outcomes with preventive interventions. We review SUDEP epidemiology and risk factors, and discuss potential measures to reduce SUDEP risk.

## Keywords

Sudden unexpected death in epilepsy (SUDEP), epilepsy, prevention, risk, seizure monitoring, surgery, vagus nerve stimulation (VNS), responsive nerve stimulation (RNS)

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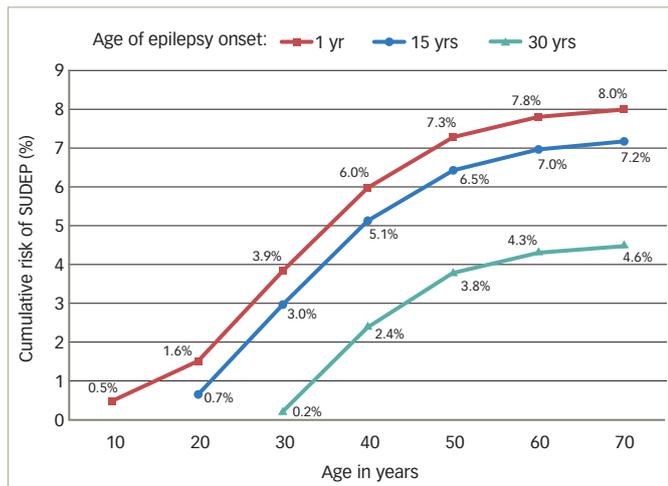
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Sudden unexpected death in epilepsy (SUDEP) is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomical cause.<sup>1</sup> It is the most common cause of death related to epilepsy and is associated with the presence, or history of, generalised tonic-clonic seizures (GTCS).<sup>2</sup> In the new classification of seizures outlined by the International League Against Epilepsy, a distinction is made between focal to bilateral tonic-clonic seizures that occur in focal epilepsies, and generalised tonic-clonic seizures that occur in generalised epilepsies.<sup>3</sup> The relevant SUDEP literature discussed in this review article was predominantly carried out prior to the introduction of the new seizure classification, and thus in general makes no such distinction. For this reason, we use the term GTCS to include both seizure categories.

Although medical treatment can achieve seizure-free status in around 70% of patients, the remaining 30% of patients have drug-resistant epilepsy, often despite polytherapy.<sup>4</sup> Continuing seizures put patients at risk of SUDEP.<sup>4</sup> Over the last few years, there has been a growing interest and research in the epidemiology, underlying causative mechanisms and prevention of SUDEP. Here we describe recent research in these areas and provide a review of the literature.

## Incidence of sudden unexpected death in epilepsy

The estimated overall crude annual incidence rate for SUDEP is 0.81 cases per 100,000 total population, ranking second only to stroke among other neurological conditions in terms of years of potential life lost.<sup>5</sup> In children and adults with epilepsy, the incidence has been estimated to be between 0.22 and 1.20 per 1,000 patient-years, respectively.<sup>6</sup> However, a recent study found a SUDEP incidence of 1.17 per 1,000 paediatric epilepsy person-years, which is comparable to incidence rates reported in adults.<sup>7</sup> The risk of sudden unexpected death among young people with epilepsy is 24–28-fold higher than in the general population.<sup>8,9</sup> The cumulative (lifetime) risk of SUDEP differs according to age of epilepsy onset; for example, epilepsy onset at age 1 year, 15 years or 30 years yield risks of 8.0%, 7.2% and 4.6%, respectively, by age 70 (*Figure 1*).<sup>5</sup> In a nationwide population-based cohort study in Sweden, the incidence of SUDEP in one year was investigated, in addition to its relationship to age, gender and psychiatric comorbidity.<sup>10</sup> Of 57,775 patients with epilepsy who were alive on 1 January 2008, 1,890 (3.3%) died during the year. The study revealed that SUDEP accounted for 5.2% of all deaths, and 36.0% of deaths in the 0–15 years age group.<sup>10</sup> Incidence of definite/probable SUDEP was 1.20 per 1,000 person years (1.41 in men and 0.96 in women).<sup>10</sup> In the <16 years, 16–50 and >50 years age groups, this incidence was 1.11, 1.13 and 1.29, respectively.<sup>10</sup> In addition, the incidence of SUDEP increased five-fold in female patients with psychiatric comorbidities, compared with female patients without them (2.34 per 1,000 person years versus 0.45 per 1,000 person years, respectively).<sup>10</sup>

Figure 1: Cumulative risk of SUDEP in epilepsy populations<sup>5</sup>

SUDEP = sudden unexpected death in epilepsy.  
Reproduced with permission from Thurman et al., 2014.<sup>5</sup>

The incidence of SUDEP varies within the epilepsy population, with the highest incidences being reported in patients referred for surgery or vagus nerve stimulation (VNS).<sup>2</sup> This is perhaps unsurprising since these patients are likely to be drug resistant. Interestingly, SUDEP rates in the US have been reported to be significantly higher in people with lower socioeconomic status, compared with those with higher incomes.<sup>11</sup>

### Classification of sudden unexpected death in epilepsy

In 1997, classification of definite, probable, possible and unlikely SUDEP was proposed based on the fulfilment of pre-specified criteria (Table 1).<sup>12</sup> Recently, a unified SUDEP classification was proposed in which additional classifications were included as follows: Definite SUDEP, Definite SUDEP Plus (includes a concomitant condition), Probable SUDEP/Probable SUDEP Plus, Possible SUDEP, Near-SUDEP/Near-SUDEP Plus, Not SUDEP and Unclassified.<sup>13</sup> Definitions for these classifications are provided in Table 2.

### Risk factors for sudden unexpected death in epilepsy

It is difficult to predict SUDEP events, however, many studies have identified certain risk factors. A combined analysis of case-control studies identified that frequency of GTCS, duration of epilepsy, young age at onset, male gender and symptomatic aetiology (usually associated with focal epilepsy), were all statistically significant risk factors.<sup>14</sup> A recent meta-analysis confirmed these findings, with the top leading risk factor for SUDEP identified as  $\geq 3$  GTCS per year.<sup>15</sup> Practice guidelines indicate that people with  $\geq 3$  GTCS per year have a 15-fold increased risk of SUDEP and that the risk is markedly increased by uncontrolled epilepsy and the absence of seizure freedom.<sup>6</sup> Identification of these factors supports clinicians in recognising those patients who may be at risk and should receive preventive treatment.

Other studies found that people with nocturnal seizures had a higher risk of SUDEP than those with a strictly diurnal seizure pattern (odds ratio: 2.6; 95% confidence interval [CI]: 1.3–5.0),<sup>16</sup> and that a lack of night-time supervision may also increase SUDEP risk.<sup>17</sup> One study identified a significant association between a prone position and SUDEP; among 253 cases, 73.3% of these patients were found dead in a prone position.<sup>18</sup> This is an interesting finding since sleeping in the prone position is also associated with an increased risk of sudden infant death syndrome, an unexplained cause of death in infancy.<sup>19</sup>

Table 1: Definition of SUDEP<sup>12</sup>

Criteria:	
1. The victim had epilepsy, defined as recurrent unprovoked seizures.	
2. The victim died unexpectedly while in a reasonable state of health.	
3. The death occurred "suddenly" (in minutes), when known.	
4. The death occurred during normal activities (e.g., in or around bed, at home, at work) and benign circumstances.	
5. An obvious medical cause of death was not found.	
6. The death was not directly caused by the seizure or status epilepticus.	
<b>Definite SUDEP</b>	Meets all above criteria, with post-mortem examination
<b>Probable SUDEP</b>	Meets all above criteria but lacks post-mortem
<b>Possible SUDEP</b>	SUDEP cannot be ruled out, but insufficient evidence regarding circumstances, and no post-mortem report available
<b>Unlikely/Not SUDEP</b>	Other causes established or circumstances make SUDEP highly improbable

SUDEP = sudden unexpected death in epilepsy.

Table 2: Classification of SUDEP<sup>13</sup>

<b>Definite SUDEP*</b>	Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration $\geq 30$ min or seizures without recovery in between), in which post-mortem examination does not reveal a cause of death
<b>Definite SUDEP plus*</b>	Satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death
<b>Probable SUDEP/ Probable SUDEP plus*</b>	Same as Definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death
<b>Possible SUDEP*</b>	A competing cause of death is present
<b>Near SUDEP/near SUDEP plus</b>	A patient with epilepsy survives resuscitation for more than one hour after a cardiorespiratory arrest that has no structural cause identified after investigation
<b>Not SUDEP</b>	A clear cause of death is known
<b>Unclassified</b>	Incomplete information available; not possible to classify

SUDEP = sudden unexpected death in epilepsy. \*If a death is witnessed, an arbitrary cut-off of death within one hour from acute collapse is suggested.

In the MORTEMUS study, a systematic retrospective survey of 147 epilepsy-monitoring units, 16 SUDEP cases were reported (11 monitored SUDEP events and 5 non-monitored SUDEP events). At the time of event, a prone position was noted in 13 of the 16 reported cases.<sup>20</sup> Most of these patients turned to the prone position during the convulsive episode, suggesting that avoiding sleeping prone is unlikely to protect from SUDEP. All 11 of the monitored cases in the MORTEMUS study had GTCS before SUDEP followed by a short period of normal or increased heart and respiratory rates, after which a combination of central apnoea, severe bradycardia and/or transient asystole, together with post-ictal

generalised electroencephalogram (EEG) suppression (PGES). Terminal apnoea always preceded terminal asystole.<sup>20</sup>

### Pathophysiological mechanisms of sudden unexpected death in epilepsy

The exact pathophysiology of SUDEP is unknown, however, it is thought to be a combination of GTCS-induced ictal and post-ictal brainstem, respiratory, and cardiac dysfunction. A model has been proposed for the mechanism of SUDEP, in which both cardiac abnormalities and respiratory depression may play a role, in combination with arousal abnormalities during the ictal and post-ictal period.<sup>21</sup> This model is based on the hypothesis that seizures in a patient with epilepsy can activate neurons that project to the midbrain and medulla, inhibiting monoaminergic and cholinergic neurons. Seizure spread to the midbrain causes dysfunction of the ascending arousal system (AAS), including serotonergic neurons. Post-ictally, AAS inhibition could cause unresponsiveness and PGES. The arousal failure can lead to hypoventilation when the patient's face is in pillows or bedding and impaired response to hypercapnia. Seizure spread into the medulla causes dysfunction of the descending arousal system, including the component that descends to the respiratory network in the medulla. This, along with increased extracellular adenosine, may impair respiratory, cardiovascular and other autonomic control neurons, while cortical activity is suppressed. Hypoventilation during the seizure would be followed by severe post-ictal hypercapnia and hypoxia. Blood gas imbalances would then lead to bradycardia, asystole and death.<sup>21</sup>

### Risk reduction for sudden unexpected death in epilepsy

Risk reduction measures should be targeted at the known risk factors.<sup>22</sup> It is important that patients and their families are aware of the risk of SUDEP and of the lifestyle factors that can reduce the risk of seizures, in addition to medical interventions that aim to control seizures. Other important aspects include medication adherence (and instructions on how to deal with missed or late doses), sleep hygiene, alcohol consumption and the avoidance of medications that can lower the seizure threshold. Monitoring or observation should be considered for those with frequent nocturnal seizures, especially GTCS. Regular patient contact with physicians may also be an important factor in SUDEP risk reduction, since many SUDEP cases had limited contact with primary care, and even fewer had undergone a specialist epilepsy review, in the year prior to death.<sup>22</sup> Experts recommend that acceptable standards of care include access to appropriate care provided by clinicians experienced in taking a consistent and standardised approach to treating epilepsy.<sup>22</sup>

### Prevention of sudden unexpected death in epilepsy

With our current knowledge, the most reasonable approach to prevent SUDEP is by seizure control.<sup>23</sup> A meta-analysis of randomised placebo-controlled trials investigating add-on anti-epileptic drug (AED) treatment for drug-resistant epilepsy hypothesised that the incidence of definite and probable SUDEP would be lower in patients receiving AEDs at effective doses than in those receiving placebo.<sup>24</sup> One hundred and twelve trials were included in the meta-analysis, assessing a total of 21,224 patients and 5,589 patient-years. A total of 33 deaths occurred, with 20 patients receiving a SUDEP diagnosis. Of these cases, 2, 7 and 11 patients fulfilled the criteria for possible, probable and definite SUDEP. Three of the 20 SUDEP events (15%), occurred in the efficacious AED group, three (15%) occurred in the non-efficacious AED group, and 14 (70%) occurred in the placebo group. SUDEP was significantly less frequent in the efficacious AED group than in the placebo group, with an odds ratio of 0.17 (95% CI 0.05–0.57,  $p=0.0046$ ). Rates of definite or

probable SUDEP per 1,000 person-years were 0.9 (95% CI 0.2–2.7) in patients who received efficacious AED doses and 6.9 (95% CI 3.8–11.6) in those allocated to placebo. This meta-analysis indicated that treatment with adjunctive AEDs at efficacious doses may reduce the incidence of definite or probable SUDEP compared with placebo in patients with previously uncontrolled seizures, and that active treatment revision for patients with refractory epilepsy may be beneficial.<sup>24</sup>

Despite optimal medical and surgical therapy, many people with epilepsy continue to have seizures. Animal studies suggest that selective re-uptake inhibitors (SSRIs), or adenosine and opiate substances may be beneficial in reducing the risk of SUDEP.<sup>4,22,25,26</sup> Clinical studies and meta-analyses suggest that SSRIs reduce the risk of epileptic seizures in patients with epilepsy and/or depression.<sup>27–30</sup> However, it should be noted that SSRIs can display pro-convulsant properties at toxic doses.<sup>31</sup> Demonstrating the efficacy of new therapies is problematic given the low rates of SUDEP; and clinical trials would need large numbers of patients to demonstrate statistical significance.

An alternative approach for SUDEP prevention might be the use of seizure monitoring devices that are equipped with sensors that alert family members or caretakers when a seizure is detected.<sup>32</sup> There are many methods to detect seizures, including scalp and intracranial EEG, electrocardiography, accelerometry, motion sensors, electrodermal activity and audio/video capture techniques.<sup>33</sup> Some methods are invasive and sensitivity may vary between them. There are no large-scale studies comparing different devices and it is difficult to determine which offers the best balance of sensitivity and specificity.<sup>33,34</sup> Further, many devices detect seizure-related motion and the systems may have several limitations including false positives and compliance issues, which could limit device utility. In addition, no devices can distinguish habitual seizures from life-threatening seizures. Finally, for many patients with treatment-resistant epilepsy who live alone, the nearest caretaker may be too far away or unavailable. Either with or without prompt post-ictal attention, some cases will progress to SUDEP.<sup>35,36</sup>

An intracranial electroencephalographic monitoring device showed high sensitivity and specificity and could detect non-convulsive seizures in a small first-in-man study ( $n=15$ ). However, the device required surgical implantation, maintenance of electrodes, and was associated with serious adverse events in 27% of patients (4/15) during the first year following implantation.<sup>37</sup> More invasive solutions, such as subdural or epidural electrodes, may not be broadly applicable.

Non-invasive alternatives for seizure monitoring include accelerometers, mattress sensors, a surface electromyography device and video motion analysis.<sup>38–41</sup> These methods detect convulsive seizures, however, they may be limited to specific environments (e.g. video and mattress devices).

Other physiological parameters that may help detect seizures include: heart rate rises (ictal tachycardia),<sup>42</sup> cardiac rhythm and conduction abnormalities,<sup>43</sup> changes in pulse oximetry (arterial oxygen saturation [SaO<sub>2</sub>] decreases in 33% of all seizures in adults)<sup>42,44</sup> and galvanic skin response or electrodermal activity/response (a measure of sympathetic system function, specifically sweat glands, which may surge during a seizure).<sup>45</sup> Monitoring these parameters is relatively inexpensive and non-invasive, and may detect the most dangerous seizures i.e. those causing autonomic dysfunction. However, these assessments lack specificity and will require sophisticated algorithms to accurately respond to an individual's seizures. An important consideration for these

devices is that they should not only improve seizure detection, but also patient quality of life. Frequent disturbance by an alarm at night may have a detrimental impact on the quality-of-life of patients and carers.<sup>34</sup>

Multimodal detectors that combine different parameters, e.g. heart rate and accelerometry, may improve the specificity of detectors but would depend on the reliability of the associated detection algorithm.<sup>33,34</sup> The advent of smartphones, smartwatches and tablets has created a new market for non-EEG seizure detection applications (recently reviewed by Van de Vel et al. 2016).<sup>46</sup> A widely used device is the Embrace Alert system (Empatica Inc., Cambridge, MA, US), which combines electrodermal activity detection, accelerometry and temperature measurements.<sup>47</sup> The Embrace Alert system has high accuracy, sensitivity and low false alarm rates in a multicentre study.<sup>48</sup> It was recently approved by the Food and Drug Administration (FDA), enabling clinicians to prescribe this device for appropriate patients. Another device, the EpiLert system (BioLert, Inc., Dallas, TX, US), is available for purchase; however, the FDA has not approved this for use in patients. Many other devices are in various stages of development, and it appears that the most effective seizure detection systems are multimodal.<sup>46</sup> While many of these devices look promising, it remains to be seen whether they will be effective in SUDEP prevention.

A recently published case report describes a probable SUDEP in a 20-year-old male patient with treatment-resistant epilepsy and 3–4 GTCS a year.<sup>35</sup> The event was recorded by an Empatica smartwatch, which issued an alert to a caregiver who arrived 15 minutes later; unfortunately the patient was found pulseless, face in pillow and despite 15 minutes of attempted CPR, was unable to be revived. Data from the smartwatch device showed convulsive movements lasting 94 seconds, and increased breathing rate coinciding with an unusually large post-ictal electrodermal response, followed by unusually irregular breathing or breathing cessation following the seizure. These data support autonomic and cerebral dysfunction as SUDEP mechanisms, in addition to sympathetic hyperactivity and prolonged PGES before death.<sup>35</sup> This case highlights a key issue with such devices; although the smartwatch was able to trigger an alert, it did not prevent SUDEP in this instance.

### Biomarkers for patients at risk of sudden unexpected death in epilepsy

There is a need for biomarkers to screen and detect patients with treatment-resistant epilepsy, and identify those at risk of SUDEP. Electrophysiological biomarkers may be useful too. Postictal generalised electroencephalographic suppression in SUDEP may be related to loss of protective reflexes and could be a surrogate marker of brainstem dysfunction, both respiratory and cardio-regulatory.<sup>20,49</sup> In a single-centre case control study of 10 patients at an epilepsy monitoring unit, the duration of PGES was found to be associated with SUDEP risk.<sup>49</sup> If all seizures were examined, prolonged PGES (>50 seconds) was associated with significantly elevated risk for SUDEP, which increased as the duration of PGES increased. When only tonic-clonic seizures were examined, PGES >20 seconds was associated with significantly higher risk.<sup>49</sup> This was a small study of refractory patients and the results may not be applicable to patients with generalised epilepsies or new onset disease. It did not measure respiratory effort so it is difficult to distinguish cause and effect.

It is difficult to determine the independent contribution of PGES to SUDEP risk in small studies. Subsequent retrospective studies have investigated the association between PGES and GTCS, as GTCS is the largest driver of SUDEP risk.<sup>50,51</sup> Investigation of 122 seizures in a study that included 57 individuals revealed that PGES is associated with generalised

seizures.<sup>51</sup> Another study aimed to identify the clinical determinants of occurrence of PGES after generalised convulsive seizures (GCS) and included 99 GCS in 69 patients. PGES was associated with tonic-clonic GCS with bilateral and symmetric tonic arm extension (type 1;  $p < 0.001$ ), clonic GCS without tonic arm extension or flexion (type 2) and GCS with unilateral or asymmetric tonic arm extension or flexion (type 3). In type 1 GCS, the risk of PGES was significantly increased when the seizure occurred during sleep (odds ratio 5.0, 95% CI 1.2–20.9) and when oxygen was not administered early (odds ratio 13.4, 95% CI 3.2–55.9).<sup>50</sup>

Autonomic dysfunction may also be a biomarker to help identify patients at risk of SUDEP. A small study of 19 patients found a correlation between heart rate variability and clinical risk factors for SUDEP.<sup>52</sup> In addition, a case report noted progressive deterioration in heart rate variability prior to SUDEP.<sup>53</sup> However, a small case-control trial failed to confirm this association.<sup>54</sup> A retrospective study of 21 patients found an association between ictal tachycardia and increased SUDEP risk.<sup>55</sup> Furthermore, another study found that when comparing abnormal ventricular conduction diagnosis and pattern (QRS <110 msec, morphology of incomplete right or left bundle branch block or intraventricular conduction delay) it was possible to distinguish 12 SUDEP cases from 22 matched controls.<sup>56</sup> Other potential biomarkers include inter-ictal and peri-ictal cardiac and autonomic dysfunction.<sup>57</sup>

Genetic factors may also help identify patients at risk of SUDEP. A study of 61 SUDEP cases found clinically relevant mutations in cardiac arrhythmia (22%) and epilepsy (25%) genes.<sup>58</sup> Whole exomes derived from epilepsy surgical tissue compared eight SUDEP cases and seven living controls and also found definite pathogenic or candidate variants in genes involved in neuro-excitability and cardiac rhythm.<sup>59</sup> Studies in animal models and patient groups have identified at least nine different brain-heart genes that may contribute to a genetic susceptibility for SUDEP.<sup>60</sup> Most genetic studies to date have identified defects in ion channel genes or genes modulating ion channel function that predispose humans and/or animal models to both seizures and fatal cardiac arrhythmias.<sup>61</sup> Other genetic defects may include 5HT, purinergic or autonomic systems.<sup>61</sup>

### Clinical trial surrogate endpoints

Measurable physiological parameters related to SUDEP could act as surrogate endpoints in clinical trials to assess therapeutic interventions. Many derangements in cardiac, autonomic, cerebral and pulmonary function have been identified in humans undergoing video-EEG telemetry. These include post-ictal oxygen saturation,<sup>44</sup> ictal or post-ictal heart rate changes (heart rate elevation, QTc changes,<sup>55,62</sup> post-ictal EEG suppression,<sup>49</sup> post-ictal decreased cerebral blood flow,<sup>63</sup> post-ictal autonomic dysfunction<sup>64,65</sup> and post-ictal hypotension.<sup>65</sup> All of these parameters have also been observed in the terminal cascade of monitored SUDEPs but validation studies are needed.

Devices that measure multimodal physiological signals can identify biomarkers and potentially at-risk individuals. Inexpensive sensors can be employed in large studies to determine the relationship between certain seizure-related signals and actual SUDEP. For example, wrist-based sensors that record electrodermal activity and heart rate to create an autonomic function signature of seizures. Such monitoring was used in a study of 34 seizures in 11 children and showed increased sympathetic activity was correlated with PGES duration, suggesting an interplay of this measure with another possible SUDEP biomarker.<sup>64</sup> The feasibility of future device trials will depend on identifying high-risk individuals through biomarkers and/or using validated surrogate endpoints.<sup>66</sup>

## Epilepsy surgery and sudden unexpected death in epilepsy

As seizure control is the most reasonable approach to reduce the risk of SUDEP, epilepsy surgery to reduce seizure frequency may also reduce the risk of SUDEP.<sup>67</sup> This was suggested in a study of 583 patients undergoing a neurosurgical procedure for refractory epilepsy. Procedures included resection, multiple subpial transection and partial or complete corpus callosum section. SUDEP was significantly associated with seizure control ( $p=0.001$ ) over an average follow-up duration of  $4.9 \pm 3.2$  years. Of 19 deaths, 18 occurred in patients who had one or more recurrent seizures, thus risk of SUDEP was significantly reduced if patients were seizure-free post-surgery.<sup>68</sup> In another study that included 305 patients who underwent temporal lobe epilepsy surgery over a 20-year period, SUDEP rates were lower than those reported for similar patient populations with chronic epilepsy.<sup>69</sup> However, the above studies do not demonstrate that the differences observed in post-operative SUDEP incidence between seizure-free and non-seizure free patients is the consequence of surgery. Indeed, it might be that the SUDEP risk in these two populations already differed prior to surgery, possibly due to larger epileptogenic zones involving autonomic-related brain regions, such as the insula, in patients who failed surgery.<sup>70</sup>

In a Swedish population-based, non-randomised, cohort study of pharmaco-resistant epilepsies, surgically treated and non-surgically treated patient populations were compared. SUDEP incidence was 2.4 per 1,000 person-years (95% CI 0.9–5.3) following epilepsy surgery versus 6.3 per 1,000 person-years (95% CI 1.7–16.1) in non-surgery patients; the observed difference was not statistically significant.<sup>71</sup> It was difficult to demonstrate an association between mortality rates and seizure outcomes two years after surgery due to the size of the cohort and limited number of deaths. However, record review revealed that none of the SUDEP cases was seizure-free at the time of death, regardless of seizure outcome two years after surgery.<sup>71</sup>

## Vagus nerve stimulation and sudden unexpected death in epilepsy

Stimulation of the vagus nerve through the implantation of a device that releases electrical impulses is a useful treatment to reduce seizure frequency in drug-resistant epilepsy. Several randomised controlled trials (RCTs) investigating the efficacy of VNS have been published.<sup>72–76</sup> Findings from two key blinded RCTs led to the approval of VNS by the FDA in patients with drug-resistant epilepsy. These two RCTs showed that seizure frequency decreased by 28–31% in the high-frequency stimulation treatment groups versus 11–15% in the low frequency stimulation groups over a 3-month period.<sup>73,74</sup>

A review of a prospectively created database looked at 436 consecutive patients with focal and generalised treatment-resistant epilepsy who underwent VNS implantation between November 1997 and April 2008 and who were followed-up.<sup>77</sup> The mean age of patients in the database was  $29.0 \pm 16.5$  years (range 1–76 years) at the time of implantation. Mean seizure frequency significantly improved by 55.8% ( $p<0.0001$ ), and  $\geq 50.0\%$  improvement in seizure control was achieved in 63.8% of patients.

While VNS helps reduce the frequency of GTCS, its impact on SUDEP remains uncertain. A cohort study of 1,819 patients revealed that the rate of SUDEP in those receiving VNS was 5.5 per 1,000 over the first two years of follow-up, but only 1.7 per 1,000 after two years.<sup>78</sup> However, a subsequent study in 466 patients did not confirm the finding.<sup>79</sup> This issue was more recently assessed in a long-term surveillance study that included 40,443 patients with VNS therapy who were followed for up

to 10 years post implantation. The aim of the study was to investigate whether SUDEP rates decreased post implantation. There were 277,661 patient-years of follow-up with a median duration of 7.6 years.<sup>80</sup> Of the 3,689 deaths in the cohort during the follow-up period, 632 were attributed to SUDEP. The analysis revealed that SUDEP risk significantly decreases during long-term follow-up of patients post VNS implantation. SUDEP rates were 2.47/1,000 for years 1–2 of follow-up compared with 1.68/1,000 for years 3–10 of follow-up (rate ratio 0.68; 95% CI 0.53–0.87;  $p=0.002$ ).<sup>80</sup> The findings translate to a 25% reduction in SUDEP events expected in this cohort under the hypothesis of stable age-adjusted SUDEP rates during follow-up, although the direct role of VNS therapy of reduction in SUDEP rates couldn't be determined in this analysis due to the lack of a control group for comparison. The authors conclude that the findings could reflect several factors, including the impact of VNS therapy, but also natural evolution and attrition, aging or changes in medication. Indeed, other studies suggest that SUDEP rates might decrease as a function of time or duration of follow-up, irrespective of any intervention. Specifically, the risk of SUDEP over time has been recently studied in two populations. Firstly, investigation of medical examiner-investigated SUDEP rates over time in the US revealed a significant decrease in 2014–15 compared with 2009–10, possibly reflecting improved epilepsy care, or natural attrition.<sup>11</sup> In another recent study of SUDEP risk in 60,952 Swedish patients with epilepsy, the incidence of SUDEP decreased with the duration of follow-up, for unknown reasons.<sup>81</sup> These findings have implications for the design of studies aiming to assess the effectiveness of interventions against SUDEP, which need to include a control group for comparison.<sup>81</sup>

## Responsive nerve stimulation and sudden unexpected death in epilepsy

An alternative therapy for drug-resistant epilepsy includes brain-responsive nerve stimulation. This is an intracranial closed loop system that provides responsive stimuli to seizure foci.<sup>82</sup> The approach was assessed in a large double-blind RCT in which seizure frequency decreased by 38% in the responsive nerve stimulation (RNS)<sup>83</sup> treatment groups versus 17% in the sham group over a 12-week blinded evaluation period.<sup>83</sup> By reducing seizure frequency, the RNS system could potentially reduce SUDEP risk. SUDEP incidence and features were investigated in a recent study in patients treated with the RNS system.<sup>84</sup> Among 707 patients (2,208 patient post-implantation years, there were 14 deaths, including four definite, two possible and one probable SUDEP.<sup>84</sup> The SUDEP rate of 2.0/1,000 patient-stimulation-years for patients treated with the RNS system is favourable relative to treatment-resistant epilepsy patients randomised to placebo in clinical studies (SUDEP rate of 6.1 per 1,000 patient-years) and patients with recurrent seizures after epilepsy surgery (6.3 per 1,000 patient-years).<sup>84</sup> Data obtained from SUDEP events in patients treated with the RNS system point to heterogeneous causative mechanisms.

## Conclusions

Despite an increasing focus on SUDEP in recent times, much more work needs to be done before the pathophysiology, risk factors and optimal prevention strategies can be better understood. In the meantime, risk-reduction strategies aimed at seizure monitoring and nocturnal monitoring, in addition to epilepsy surgery, optimising AED therapy and VNS or RNS to reduce seizure frequency, are of paramount importance. Furthermore, increasing awareness of SUDEP among treatment-resistant epilepsy patients and their families/carers, particularly those with GTCS, is imperative, so that they are fully informed of the risks, modifiable factors and treatment options. Such improved practice, initiatives and interventions are likely to reduce the future toll of SUDEP further. □

1. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia*. 1997;38:56–8.
2. Devinsky O, Hesdorffer DC, Thurman DJ, et al. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol*. 2016;15:1075–88.
3. Fisher RS. The new classification of seizures by the International League Against Epilepsy 2017. *Curr Neurol Neurosci Rep*. 2017;17:48.
4. Maguire MJ, Jackson CF, Marson AG, et al. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). *Cochrane Database Syst Rev*. 2016;7:CD011792.
5. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. *Epilepsia*. 2005;59:1479–85.
6. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2017;88:1674–80.
7. Keller AE, Whitney R, Li SA, et al. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology*. 2018;91:e107–e11.
8. Holst AG, Winkel BG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia*. 2013;54:1613–20.
9. Ficker DM, So EL, Shen WK, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology*. 1998;51:1270–4.
10. Sveinsson O, Andersson T, Carlsson S, et al. The incidence of SUDEP: A nationwide population-based cohort study. *Neurology*. 2017;89:170–7.
11. Cihan E, Hesdorffer DC, Brandson M, et al. Socioeconomic disparities in US epilepsy mortality rates based on medicolegal investigations. American Epilepsy Society, 2017; Abstract 3.404. Available at: [www.aesnet.org/meetings\\_events/annual\\_meeting\\_abstracts/view/349847](http://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/349847) (accessed 15 July 2018).
12. Annegers JF. United States perspective on definitions and classifications. *Epilepsia*. 1997;38:S9–12.
13. Nashef L, So EL, Ryvlin P, et al. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia*. 2012;53:227–33.
14. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. *Epilepsia*. 2011;52:1150–9.
15. DeGiorgio CM, Markovic D, Mazumder R, et al. Ranking the leading risk factors for sudden unexpected death in epilepsy. *Front Neurol*. 2017;8:473.
16. Lamberts RJ, Thijs RD, Laffan A, et al. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia*. 2012;53:253–7.
17. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology*. 2005;64:1131–3.
18. Liebenthal JA, Wu S, Rose S, et al. Association of prone position with sudden unexpected death in epilepsy. *Neurology*. 2015;84:703–9.
19. Sperhake J, Jorch G, Bajanowski T. The prone sleeping position and SIDS. Historical aspects and possible pathomechanisms. *Int J Legal Med*. 2018;132:181–5.
20. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol*. 2013;12:966–77.
21. Massey CA, Sowers LP, Dlouhy BJ, et al. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. *Nat Rev Neurol*. 2014;10:271–82.
22. Watkins L, Shankar R, Sander JW. Identifying and mitigating Sudden Unexpected Death in Epilepsy (SUDEP) risk factors. *Expert Rev Neurother*. 2018;18:265–74.
23. Ryvlin P, Rheims S. Epilepsy: new epidemiological and therapeutic perspectives. *Lancet Neurol*. 2012;11:5–7.
24. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol*. 2011;10:961–8.
25. Hernandez EJ, Williams PA, Dudek FE. Effects of fluoxetine and TFMP on spontaneous seizures in rats with pilocarpine-induced epilepsy. *Epilepsia*. 2002;43:1337–45.
26. Vermoesen K, Massie A, Smolders I, et al. The antidepressants citalopram and reboxetine reduce seizure frequency in rats with chronic epilepsy. *Epilepsia*. 2012;53:870–8.
27. Bateman LM, Li CS, Lin TC, et al. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. *Epilepsia*. 2010;51:2211–4.
28. Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry*. 2007;62:345–54.
29. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants: a systematic review and meta-analysis. *Drug Saf*. 2008;31:851–65.
30. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract*. 2005;59:1435–40.
31. Kanner AM. Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence. *Epilepsy Behav*. 2016;61:282–6.
32. Ryvlin P, Ciumas C, Wisniewski I, et al. Wearable devices for sudden unexpected death in epilepsy prevention. *Epilepsia*. 2018;59 Suppl 1:61–6.
33. Ramgopal S, Thome-Souza S, Jackson M, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy Behav*. 2014;37:291–307.
34. Jory C, Shankar R, Coker D, et al. Safe and sound? A systematic literature review of seizure detection methods for personal use. *Seizure*. 2016;36:4–15.
35. Picard RW, Migliorini M, Caborni C, et al. Wrist sensor reveals sympathetic hyperactivity and hypoventilation before probable SUDEP. *Neurology*. 2017;89:633–5.
36. Swingthamer J, Devinsky O, Friedman D. Can post-ictal intervention prevent sudden unexpected death in epilepsy? A report of two cases. *Epilepsy Behav*. 2012;24:377–9.
37. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol*. 2013;12:563–71.
38. Nijsen TM, Arends JB, Griep PA, et al. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. *Epilepsy Behav*. 2005;7:74–84.
39. Fulton S, Poppel KV, McGregor A, et al. Prospective study of 2 bed alarms for detection of nocturnal seizures. *J Child Neurol*. 2013;28:1430–3.
40. Conradtsen I, Beniczky S, Wolf P, et al. Evaluation of novel algorithm embedded in a wearable sEMG device for seizure detection. *Conf Proc IEEE Eng Med Biol Soc*. 2012;2012:2048–51.
41. Karayiannis NB, Tao G, Xiong Y, et al. Computerized motion analysis of videotaped neonatal seizures of epileptic origin. *Epilepsia*. 2005;46:901–17.
42. Moseley BD, Wirrell EC, Nickels K, et al. Electrocardiographic and oximetric changes during partial complex and generalized seizures. *Epilepsy Res*. 2011;95:237–45.
43. Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. *Epilepsia*. 2000;41:542–8.
44. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain*. 2008;131:3239–45.
45. Poh MZ, Loddenkemper T, Swenson NC, et al. Continuous monitoring of electrodermal activity during epileptic seizures using a wearable sensor. *Conf Proc IEEE Eng Med Biol Soc*. 2010;2010:4415–8.
46. Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure detection systems and potential SUDEP prevention: State of the art: Review and update. *Seizure*. 2016;41:141–53.
47. Onorati F, Regalia G, Caborni C, et al. Improvement of a convulsive seizure detector relying on accelerometer and electrodermal activity collected continuously by a wristband. Presented at the 2016 Epilepsy Pipeline Conference, San Francisco, California, 25–26 February 2016.
48. Onorati F, Regalia G, Caborni C, et al. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. *Epilepsia*. 2017;58:1870–9.
49. Lhatoo SD, Faulkner HJ, Demby K, et al. An electroclinical case-control study of sudden unexpected death in epilepsy. *Ann Neurol*. 2010;68:787–96.
50. Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. *Neurology*. 2015;85:1598–603.
51. Surges R, Strzelczyk A, Scott CA, et al. Postictal generalized electroencephalographic suppression is associated with generalized seizures. *Epilepsy Behav*. 2011;21:271–4.
52. DeGiorgio CM, Miller P, Meyrmandi S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. *Epilepsy Behav*. 2010;19:78–81.
53. Rauscher G, DeGiorgio AC, Miller PR, et al. Sudden unexpected death in epilepsy associated with progressive deterioration in heart rate variability. *Epilepsy Behav*. 2011;21:103–5.
54. Surges R, Adjei P, Kallis C, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. *Epilepsia*. 2010;51:233–42.
55. Nei M, Ho RT, Abou-Khalil BW, et al. EEG and ECG in sudden unexplained death in epilepsy. *Epilepsia*. 2004;45:338–45.
56. Chyou JY, Friedman D, Cerrone M, et al. Electrocardiographic features of sudden unexpected death in epilepsy. *Epilepsia*. 2016;57:e135–9.
57. Jansen K, Lagae L. Cardiac changes in epilepsy. *Seizure*. 2010;19:455–60.
58. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Ann Neurol*. 2016;79:522–34.
59. Friedman D, Kannan K, Faustin A, et al. Cardiac arrhythmia and neuroexcitability gene variants in resected brain tissue from patients with sudden unexpected death in epilepsy (SUDEP). *NPJ Genom Med*. 2018;3:9.
60. Glasscock E. Genomic biomarkers of SUDEP in brain and heart. *Epilepsy Behav*. 2014;38:172–9.
61. Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. *J Neurol Neurosurg Psychiatry*. 2016;87:402–13.
62. Surges R, Scott CA, Walker MC. Enhanced QT shortening and persistent tachycardia after generalized seizures. *Neurology*. 2010;74:421–6.
63. Moseley BD, Britton JW, Nelson C, et al. Periictal cerebral tissue hypoxemia: a potential marker of SUDEP risk. *Epilepsia*. 2012;53:e208–11.
64. Poh MZ, Loddenkemper T, Reinsberger C, et al. Autonomic changes with seizures correlate with postictal EEG suppression. *Neurology*. 2012;78:1868–76.
65. Bozorgi A, Chung S, Kaffashi F, et al. Significant postictal hypotension: expanding the spectrum of seizure-induced autonomic dysregulation. *Epilepsia*. 2013;54:e127–30.
66. Devinsky O, Ryvlin P, Friedman D. Preventing sudden unexpected death in epilepsy. *JAMA Neurol*. 2018;75:531–2.
67. Jehi L, Najm IM. Sudden unexpected death in epilepsy: impact, mechanisms, and prevention. *Cleve Clin J Med*. 2008;75 Suppl 2:S66–70.
68. Sperling MR, Harris A, Nei M, et al. Mortality after epilepsy surgery. *Epilepsia*. 2005;46 Suppl 11:49–53.
69. Hennessy MJ, Langan Y, Elwes RD, et al. A study of mortality after temporal lobe epilepsy surgery. *Neurology*. 1999;53:1276–83.
70. Ryvlin P, Montavont A. [Does epilepsy surgery really lower mortality?] *Neurochirurgie*. 2008;54:282–6.
71. Nilsson L, Ahlborn A, Farahmand BY, et al. Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia*. 2003;44:575–81.
72. Aihua L, Lu S, Liping L, et al. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. *Epilepsy Behav*. 2014;39:105–10.
73. Ben-Menachem E, Manon-Espallat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. 1994;35:616–26.
74. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998;51:48–55.
75. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. 2012;54:855–61.
76. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLSE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. 2014;55:893–900.
77. Elliott RE, Morsi A, Kalhorn SP, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav*. 2011;20:57–63.
78. Annegers JF, Coan SP, Hauser WA, et al. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia*. 2000;41:549–53.
79. Granbichler CA, Nashef L, Selway R, et al. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. *Epilepsia*. 2015;56:291–6.
80. Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia*. 2018;59:562–72.
81. Tomson T, Sveinsson O, Carlsson S, et al. Evolution over time of SUDEP incidence: A nationwide population-based cohort study. *Epilepsia*. 2018;59(8):e120–e124.
82. Kwon CS, Ripa V, Al-Awar O, et al. Epilepsy and neuromodulation-randomized controlled trials. *Brain Sci*. 2018;8(4):pii:E69.
83. Morrell MJ, Group RNSSES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011;77:1295–304.
84. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. *Epilepsia*. 2018;59:555–61.