Sudden unexpected death in epilepsy: current knowledge and future directions

Torbjörn Tomson, Lina Nashef, Philippe Ryvlin

Although largely neglected in earlier literature, sudden unexpected death in epilepsy (SUDEP) is the most important epilepsy-related mode of death, and is the leading cause of death in people with chronic uncontrolled epilepsy. Research during the past two to three decades has shown that incidence varies substantially depending on the epilepsy population studied, ranging from 0·09 per 1000 patient-years in newly diagnosed patients to 9 per 1000 patient-years in candidates for epilepsy surgery. Risk profiles have been delineated in case-control studies. These and other studies indicate that SUDEP mainly occurs in the context of a generalised tonic-clonic seizure. However, it remains unclear why a seizure becomes fatal in a person that might have had many similar seizures in the past. Here, we review SUDEP rates, risk factors, triggers, and proposed mechanisms, and critically assess potential preventive strategies. Gaps in knowledge are discussed and ways forward are suggested.

Introduction

People with epilepsy are well known to be at increased risk of sudden death. Although early mortality series at the beginning of the 20th century reported deaths from status epilepticus to be more common, deaths associated with single seizures were also recognised. In 1904, Spratling wrote of epilepsy as a disease that, “destroys life suddenly and without warning through a single, brief attack...and does so in from 3 to 4% of all who suffer from it”. Yet, the occurrence of such events was later disputed and epileptic convulsions were often said to seem worse than they actually were. There has been increased awareness of sudden unexpected death in epilepsy (SUDEP) over the past two to three decades, and what was once disputed is now acknowledged as a serious problem in epilepsy. Yet despite this awareness, systematic well funded research remains limited. The medical literature contains much repetition, with effort spent on re-analysing data with substantial methodological limitations. There is also a tendency to assume that SUDEP is a risk for only those with intractable epilepsy, to some extent ignoring the larger group of individuals with better but not fully controlled epilepsy who have a lower, but nevertheless real, risk of SUDEP.

We aim to provide an update on the incidence of SUDEP in different epilepsy populations, review known risk factors, and discuss possible SUDEP mechanisms and strategies for prevention. We also discuss the gaps in current knowledge and suggest future research directions.

Definitions of SUDEP

The lack of a pathological cause of death and the un witnessed nature of many SUDEP deaths pose difficulties with regard to definitions of SUDEP, which describe a category and not a mechanism or condition per se. SUDEP is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom post-mortem examination does not reveal a structural or toxicological cause for death. This workable SUDEP definition is adopted widely but not universally. Although it has proved useful, the definition has conceptual and practical limitations. A narrow definition that excludes potentially life-threatening concomitant pathological processes, although useful in research into a pure SUDEP category, does not allow for an assessment of increased risk associated with epilepsy if there is coexisting disease.

In epidemiological studies, particularly if data are incomplete and autopsy has not been done, an agreed classification system allows categorisation of deaths observed. Cases that fulfil the above definition fall into the category of “definite SUDEP”, and sudden deaths occurring in benign circumstances with no known competing cause for death but without autopsy are classified as “probable SUDEP”. Cases in which SUDEP cannot be excluded, either because of limited information about the circumstances of death or because there is a plausible competing explanation for death, are classified as “possible SUDEP”.

Incidence of SUDEP

A widely quoted population-based study from Rochester, MN, USA, found that the rate of sudden unexplained death in the epilepsy population exceeded the expected rate in the general population by nearly 24 times, with a standardised mortality ratio of 23·7 (95% CI 7·7–55·0). The quoted overall incidence was 0·35 per 1000 person-years, but this was based on only nine SUDEP cases among 535 total deaths with six deaths unclassified. The risk of SUDEP is clearly increased in the general epilepsy population, but the reported incidence varies widely, depending on criteria and definitions, study methods, and in particular on the type of epilepsy population under study. Community-based studies provide the most representative estimates. Results of such studies are summarised in table 1. The least biased data come from analysis of causes of death among unselected cohorts of incident cases of epilepsy with the lowest risk estimates, with incidences ranging from 0·09 to 0·35 per 1000 person-years. However, extrapolating such figures
to prevalent epilepsy cases is inappropriate. More commonly, SUDEP cases are ascertained through review of post-mortem records of the coroner or medical examiner. Incidence is then calculated on the basis of an assumed prevalence of epilepsy in the coroner’s catchment area. These estimates are less reliable. Reported incidence in a prevalence population is higher than in incidence cohorts at 0·9–2·3 per 1000 person-years (table 1). Another method uses databases of antiepileptic drug (AED) prescriptions to identify people with presumed epilepsy and to review causes of death. The incidences of 0·54 and 1·3 per 1000 person-years are indicative of a prevalent population.6,7

The most common approach is to identify cases of SUDEP among cohorts of patients with epilepsy from hospital records, epilepsy clinics, and referral centres, or from databases on clinical trials of AEDs (table 2). The risk among patients with presumably chronic, often refractory, epilepsy is higher (1·1–5·9 per 1000 person-years). The highest risk has been reported among epilepsy surgery candidates or patients who continue to have seizures after surgery (6·3–9·3 per 1000 person-years; table 2).26–29

Table 1: Community-based studies of the incidence of SUDEP

<table>
<thead>
<tr>
<th>Country Study population</th>
<th>Case ascertainment</th>
<th>Cases (n)</th>
<th>Total person-years</th>
<th>SUDEP incidence (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ficker and co-workers4 USA Community Retrospective review of deaths in all epilepsy patients in Rochester (MN)</td>
<td>9</td>
<td>25 940</td>
<td>0·35</td>
<td></td>
</tr>
<tr>
<td>Lhatoo and co-workers5 UK Community Prospective follow-up of newly diagnosed epilepsy cohort</td>
<td>1</td>
<td>11 400</td>
<td>0·09</td>
<td></td>
</tr>
<tr>
<td>Jick and co-workers6 USA AED prescription database, age 15–49 years Retrospective review of deaths</td>
<td>11</td>
<td>8 460</td>
<td>1·3</td>
<td></td>
</tr>
<tr>
<td>Tennis and co-workers7 Canada AED prescription database, age 15–49 years Retrospective review of deaths</td>
<td>18</td>
<td>33 299</td>
<td>0·54</td>
<td></td>
</tr>
<tr>
<td>Terrence and co-workers6 USA Community Retrospective review of autopsy records in medical examiner’s office</td>
<td>37</td>
<td>–</td>
<td>0·9</td>
<td></td>
</tr>
<tr>
<td>Leestma and co-workers8 USA Community Retrospective review of autopsy records in medical examiner’s office</td>
<td>66</td>
<td>–</td>
<td>1·9</td>
<td></td>
</tr>
<tr>
<td>Langan9 Ireland Community Prospective ascertainment from medical examiner</td>
<td>60</td>
<td>–</td>
<td>2·3</td>
<td></td>
</tr>
<tr>
<td>Opeskin and co-workers10 Australia Community Prospective ascertainment from coroner’s office</td>
<td>50</td>
<td>–</td>
<td>1·3</td>
<td></td>
</tr>
</tbody>
</table>

If information on actual number of person-years was not available, incidence was estimated on the basis of an assumed epilepsy prevalence of 0·5% in the population served by the medical examiner/coroner. AED=antiepileptic drug. ··=not available.

Table 2: Studies of the incidence of SUDEP in selected epilepsy populations

<table>
<thead>
<tr>
<th>Country Study population</th>
<th>Case ascertainment</th>
<th>Cases (n)</th>
<th>Total person-years</th>
<th>SUDEP incidence (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson and co-workers13 Sweden Epilepsy cohort from hospital discharge register Retrospective</td>
<td>62</td>
<td>40 508</td>
<td>1·5</td>
<td></td>
</tr>
<tr>
<td>Mohanraj and co-workers14 UK Epilepsy clinic, newly diagnosed Retrospective</td>
<td>7</td>
<td>6482</td>
<td>1·1</td>
<td></td>
</tr>
<tr>
<td>Walczak and co-workers15 USA Epilepsy centres Prospective</td>
<td>20</td>
<td>16 463</td>
<td>1·2</td>
<td></td>
</tr>
<tr>
<td>Timmings16 UK Epilepsy clinic Retrospective</td>
<td>14</td>
<td>7000</td>
<td>2·0</td>
<td></td>
</tr>
<tr>
<td>Mohanraj and co-workers16 UK Epilepsy clinic, chronic patients Retrospective</td>
<td>55</td>
<td>22 935</td>
<td>2·5</td>
<td></td>
</tr>
<tr>
<td>Nash and co-workers21 UK Tertiary referral centre Retrospective</td>
<td>11</td>
<td>1849</td>
<td>5·9</td>
<td></td>
</tr>
<tr>
<td>Vlooswijk and co-workers18 Netherlands Tertiary referral centre Retrospective</td>
<td>29</td>
<td>–</td>
<td>1·2</td>
<td></td>
</tr>
<tr>
<td>Klenerman and co-workers19 UK Residential care, epilepsy Retrospective</td>
<td>7</td>
<td>3392</td>
<td>2·1</td>
<td></td>
</tr>
<tr>
<td>Nash and co-workers20 UK Residential care, epilepsy and learning disability Retrospective</td>
<td>14</td>
<td>4135</td>
<td>3·4</td>
<td></td>
</tr>
<tr>
<td>McKee and Bodfish20 USA Residential care, epilepsy and mental retardation Retrospective</td>
<td>11</td>
<td>3012</td>
<td>3·6</td>
<td></td>
</tr>
<tr>
<td>Racoosin and co-workers22 USA Refractory epilepsy, AED add-on trials Prospective</td>
<td>52</td>
<td>9144</td>
<td>3·8</td>
<td></td>
</tr>
<tr>
<td>Leestma and co-workers23 USA Refractory epilepsy, lamotrigine add-on trials Prospective</td>
<td>24</td>
<td>5747</td>
<td>3·5</td>
<td></td>
</tr>
<tr>
<td>Derby and co-workers24 UK Refractory epilepsy, &gt;2 AEDs (patients in prescription database) Retrospective</td>
<td>15</td>
<td>6784</td>
<td>2·2</td>
<td></td>
</tr>
<tr>
<td>Annegers and co-workers25 International Refractory epilepsy, vagal nerve stimulation Retrospective</td>
<td>8</td>
<td>1335</td>
<td>6·0</td>
<td></td>
</tr>
<tr>
<td>Dasheiff and co-workers26 USA Epilepsy surgery referrals Prospective</td>
<td>7</td>
<td>–</td>
<td>9·3</td>
<td></td>
</tr>
<tr>
<td>Nilsson and co-workers27 Sweden Surgery candidates not operated Prospective</td>
<td>4</td>
<td>635</td>
<td>6·3</td>
<td></td>
</tr>
<tr>
<td>Speeling and co-workers28 USA Continued seizures after surgery Prospective</td>
<td>10</td>
<td>1580</td>
<td>6·3</td>
<td></td>
</tr>
</tbody>
</table>

If information on actual number of person-years was not available, incidence was based on an estimate. AED=antiepileptic drug. ··=not available.
patients to 9·3 per 1000 person-years in epilepsy surgery candidates (figure 1). As expected for the size of the cohort, the low risk in newly diagnosed patients is supported by the absence of SUDEP among 1293 patients in initial AED monotherapy trials (983 person-years). Epilepsy in remission is another low-risk situation. The incidence of probable SUDEP was 0·4 per 1000 person-years in patients who had been seizure free for at least 2 years in the Medical Research Council AED withdrawal study.

Most of the studies summarised focus on adult patients. Four studies (not shown) specifically assessed SUDEP in children, with incidence quoted on the basis of an assumed prevalence. SUDEP accounted for 11 of 1095 deaths among children in the state of Victoria, Australia. The estimated incidence of SUDEP was 0·36 per 1000 person-years. Over a 10-year period, 27 cases aged less than 18 years were ascertained through multiple sources in Ontario, Canada (including the coroner’s office; incidence 0·2 per 1000 person-years). A Swiss hospital-based study identified four cases and estimated the incidence at 0·43 per 1000. In Nova Scotia, Canada, a long-term follow-up of a population-based cohort of 688 children who developed epilepsy reported only one SUDEP, which occurred at the age of 21 years (0·11 per 1000 person-years). Clearly, although SUDEP occurs in children, it seems to be less frequent than in adults. Children with Dravet syndrome might be an exception, and high SUDEP rates have been reported in this rare severe myoclonic epilepsy in infancy.

Risk factors identified in controlled studies

Early uncontrolled descriptive studies based on selected populations, often retrospective case series from coroner’s records, identified a risk profile for SUDEP that included young age, male sex, poor compliance with AED treatment, and chronic alcohol use. These observations are likely to be affected by selection bias and are difficult to interpret in the absence of control populations.

Risk factors have been more appropriately analysed in controlled studies, mainly by use of a retrospective case-control design. These studies, however, vary substantially in many respects, including SUDEP criteria, risk factors analysed, study populations, and selection of controls. Risk factors identified in highly selected epilepsy populations (eg, those in residential care with other handicaps) are of uncertain relevance to the general epilepsy population. Selection of the control population will also have a major effect on results. Some studies chose living patients with epilepsy as controls, whereas many have used epilepsy controls who died from other causes. The former strategy aims to identify factors that distinguish patients with epilepsy at risk, which is more clinically relevant. The outcome of case-control studies that use non-SUDEP deaths as controls is influenced by the specific causes of deaths among controls, which can vary between studies. Such studies have been claimed to be more likely to provide information on the immediate circumstances surrounding death. The ten studies that met our selection criteria and used living epilepsy controls are summarised in table 3 and comprise 366 SUDEP cases. Of six studies analysing seizure frequency, five reported that poor seizure control, in particular of generalised tonic-clonic seizures, was a significant risk factor (table 3). A Swiss hospital-based study identified four cases and estimated the incidence at 0·43 per 1000. A study in Nova Scotia, Canada, reported the incidence at 0·2 per 1000 person-years. A Swiss hospital-based study identified four cases and estimated the incidence at 0·2 per 1000. A study in Nova Scotia, Canada, reported the incidence at 0·2 per 1000 person-years. A Swiss hospital-based study identified four cases and estimated the incidence at 0·2 per 1000 person-years. A study in Nova Scotia, Canada, reported the incidence at 0·2 per 1000 person-years. 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SUDEP risks with these two AEDs have not been confirmed in other studies.

Onset of epilepsy at a young age or long duration of epilepsy was a risk factor in three studies.\textsuperscript{12,13,16} The apparent protective effect of supervision was particularly interesting. Unfortunately, this has so far been assessed in only one case-control study, but regular checks during the night or use of a listening device versus no supervision was associated with a decreased risk (OR 0·4, 0·2–0·8), as was sharing a bedroom with someone capable of giving assistance (OR 0·0–4, 0·2–0·8).\textsuperscript{29}

Studies that used non-SUDEP deaths among people with epilepsy as controls are summarised in table 4. The most common risk factors were young age, death in bed, or prone position. Evidence of a terminal seizure is also more common among SUDEP than other deaths, which is to be expected given the various non-epilepsy-related causes of death in the control group. Indications of poor compliance with prescribed AED medication were less common among SUDEPs (69%) than controls (34%).
Mechanisms underlying SUDEP
Understanding the mechanisms behind SUDEP is key to prevention. Unfortunately, we are still at a stage of hypothesis generation, although case-control studies have provided us with risk profiles and clues. Having long-standing chronic epilepsy is a factor, and different syndromes might carry different risks. Individual predisposition is clearly a factor, because only a small proportion of those with refractory epilepsy have SUDEP. SUDEP is in most cases triggered by a tonic-clonic seizure, but what are the additional factors that make this seizure fatal unlike all other previous seizures? Are these extrinsic and dependent on circumstances in which the seizure occurs, or are they intrinsic? What is the mechanism by which a seizure becomes fatal? Does it involve apnoea, cardiac arrhythmia, or cerebral electrical shutdown via cardiorespiratory mechanisms? And what treatment-related factors influence these mechanisms? The chain of circumstances that any hypothesis of SUDEP mechanisms needs to encompass is illustrated in figure 2.

Experimental data
Animal work on neuro-cardiorespiratory modulation during epileptiform activity has focused on anatomical neural specialisation and networks, and on sympathetic and parasympathetic variables. Animal models of epilepsy have provided support both for respiratory and cardiac mechanisms in SUDEP.14–16 Sudden death occurs in certain strains of mice, with sound-induced (audiogenic) seizures associated with respiratory arrest, which are preventable by oxygenation without any change in seizure severity.17 One study reported an increased incidence of ictal respiratory arrest during audiogenic seizures in a susceptible mouse strain that received the selective serotonin reuptake inhibitor fluoxetine, and an increased incidence with the serotonin antagonist cyproheptadine.18 In sheep with convulsive status epilepticus, approximately a third of animals died within 5 min due to hypoventilation, with higher peak left atrial and pulmonary artery pressures and extravascular lung water, with only benign arrhythmias noted.19 A second study in tracheostomised sheep noted central apnoea and hypoventilation in all animals.20 Three animals died, a similar proportion to the previous study. In addition to hypoventilation, one animal died of acute heart failure within 2 min of seizure onset, accompanied by histological evidence of cardiac ischaemia with similar but less marked changes in other animals.21 In an experimental hemispherectomised rat model, paroxysmal activity was induced by topical penicillin-G at hypothalamic and mesencephalic levels with a transient increase in vagal nerve firing with electrocardiographic (ECG) changes and hypotension. In some animals, co-activation was associated with increased vagal tone, cardiac arrhythmias, hyperkalaemia, acidosis, pulmonary hypertension, and death, with lung oedema observed on histological examination.22

Clinical data
Apart from risk factors, three main sources of clinical evidence could contribute to our understanding of the mechanisms of SUDEP: (1) direct observation of such deaths and of their potential precipitating factors; (2) demonstration of seizure-related and potentially fatal respiratory or cardiac dysfunction; and (3) post-mortem pathological findings.

Direct observation of SUDEP or near SUDEP
Four SUDEP cases have been reported during electroencephalographic (EEG) monitoring.57–60 Another two cases were monitored at the time of a near SUDEP, with successful resuscitation of cardiorespiratory arrest.61,62 These six cases are shown in table 5. All occurred during or immediately after a partial or secondarily generalised seizure. In three SUDEP cases, terminal flattening of the EEG seemed to occur before any fatal cardiac or respiratory arrest, as suggested by the lack of prior EEG slowing typically observed during anoxia, and the persistence of pulse artefact for several minutes after the cessation of brain activity in two cases.62–65 The fourth SUDEP case seemed to be related to a seizure-triggered ventricular fibrillation followed by terminal asystole in a patient with a past history of myocardial infarction and angina.27 However, respiration was not monitored in these four patients. In the two monitored cases of near...
### Table 5: Clinical characteristics and observations in four patients with SUDEP and two with near SUDEP occurring during monitoring

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Dasheiff and Dickinson(^\text{a}) (SUDEP(^*))</th>
<th>Bird and co-workers(^\text{a}) (SUDEP)</th>
<th>Lee and co-workers(^\text{b})(^\text{c}) (SUDEP)</th>
<th>So and co-workers(^\text{d}) (near SUDEP)</th>
<th>McLean and Wimalaratna(^\text{a}) (SUDEP)</th>
<th>Thomas and co-workers(^\text{e}) (near SUDEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, age (years)</td>
<td>Male, 48</td>
<td>Male, 47</td>
<td>Female, 41</td>
<td>Female, 20</td>
<td>Female, 50</td>
<td>Male, 18</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>27</td>
<td>19</td>
<td>Infancy</td>
<td>1</td>
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<td>14</td>
</tr>
<tr>
<td>Relevant history</td>
<td>Myocardial infarction at 38 years, angina</td>
<td></td>
<td></td>
<td>Recurrent post-ictal respiratory arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure type</td>
<td>CPS</td>
<td>CPS + 2nd GTCS</td>
<td>Partial seizures</td>
<td>CPS + 2nd GTCS</td>
<td>SPS + 2nd GTCS</td>
<td>SPS + CPS</td>
</tr>
<tr>
<td>Nocturnal seizure</td>
<td>⋯</td>
<td>Yes</td>
<td>⋯</td>
<td>⋯</td>
<td>⋯</td>
<td>⋯</td>
</tr>
<tr>
<td>EEG focus</td>
<td>Left temporal</td>
<td>Right temporal</td>
<td>Left temporal</td>
<td>Bi-frontal</td>
<td>Left temporal</td>
<td>Right temporal</td>
</tr>
<tr>
<td>AEDs at admission</td>
<td>Phenytoin, carbamazepine, phenobarbital</td>
<td>Phenytoin, carbamazepine, gabapentin</td>
<td>Phenytoin, carbamazepine, gabapentin</td>
<td>Valproate, gabapentin, felbamate</td>
<td>Valproate, lamotrigine</td>
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<tr>
<td>Monitoring data</td>
<td>Type of monitoring</td>
<td>Intracranial EEG</td>
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<td>Video and scalp EEG</td>
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<tr>
<td>Video</td>
<td>⋯</td>
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<td>EEG</td>
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<td>⋯</td>
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</tr>
<tr>
<td>Description of event</td>
<td>Type of last seizure</td>
<td>CPS</td>
<td>2nd GTCS</td>
<td>Post-ictal permanent flattening of EEG, right then left, followed by marked suppression of EEG, then bradycardia for 2 mins, then terminal asystole</td>
<td>Post-ictal central apnoea followed by bradycardia, asystole and EEG flattening after 10 s, 67 s, and 87 s, respectively</td>
<td>Polyphasic ictal discharges for 52 s followed by abrupt and terminal flattening of EEG traces</td>
</tr>
<tr>
<td>Time of event</td>
<td>Day time</td>
<td>Night time</td>
<td>Night time</td>
<td>Day time</td>
<td>Day time</td>
<td>Day time</td>
</tr>
<tr>
<td>Cluster of seizures</td>
<td>2 seizures in 1 h</td>
<td>5 seizures in &lt;24 h</td>
<td>No</td>
<td>4 seizures in 6 h</td>
<td>No</td>
<td>7 seizures in 2 h</td>
</tr>
<tr>
<td>Type of last seizure</td>
<td>CPS</td>
<td>2nd GTCS</td>
<td>2nd GTCS</td>
<td>2nd GTCS</td>
<td>Unclear</td>
<td>CPS</td>
</tr>
<tr>
<td>Supervision</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>Ineffective</td>
<td>Not done</td>
<td>Not done</td>
<td>Effective</td>
<td>Not done</td>
<td>Effective</td>
</tr>
<tr>
<td>Post-mortem findings</td>
<td>Marked lung congestion, less relevant findings</td>
<td></td>
<td>Mild lung congestion</td>
<td>No abnormality</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Cardiac arrhythmia</td>
<td>CNS shutdown</td>
<td>CNS shutdown</td>
<td>Central apnoea</td>
<td>CNS shutdown</td>
<td>Obstructive apnoea</td>
</tr>
</tbody>
</table>

SUDEP, apnoea, either central and post-ictal or ictal and obstructive, was thought to be the primary dysfunction that later led to cardiac arrest.\(^{5,6,12}\) The above data suggest that different seizure-induced interrelated mechanisms might contribute to SUDEP, including primary cerebral shutdown, cardiac arrhythmia, and central or obstructive apnoea.

Many SUDEPs have been directly observed without EEG monitoring. The proportion of SUDEPs that were witnessed varied from 7% to 38%\(^{5,12,30,32-34,41-47}\). When witnessed, a seizure, most frequently generalised tonic-clonic, was reported to occur immediately before death in 90% of cases.\(^{46}\) One study specifically searched for a history of post-ictal breathing difficulties and found confirmative evidence in most cases.\(^{47}\) However, one should remain cautious about the interpretation of such reports by non-medical witnesses.

Seizure-induced respiratory and cardiac dysfunction

Systematic monitoring of cardiorespiratory variables in 17 patients with epilepsy undergoing video EEG showed the occurrence of central apnoea of significant duration in 59% of patients, and in 20 of 47 seizures, either complex partial, tonic, or generalised tonic-clonic.\(^{69}\) Obstructive apnoea was also noted, but might have been observed less frequently in a monitored environment, as was transient bradycardia or sinus arrest, which in three of four patients was associated with central apnoea. Apnoea might also represent the only ictal symptom of temporal lobe seizures, especially in children.\(^{69,71}\) Ictal bradycardia and sinus arrest have also been described in many case reports.\(^{2}\) The occurrence of ictal asystole was assessed in three large series of patients undergoing long-term video-EEG monitoring, and 2.7–4.0 per 1000 monitored patients had at least one
The proportion of patients with ictal asystole might be much higher if monitoring is extended. A prospective long-term ECG study was undertaken in 20 patients with refractory partial epilepsy who received an implantable loop recorder. 220 000 patient-hours were monitored during 24 months. Although only a small proportion of seizures for every patient was associated with significant cardiac events, ictal asystole of at least 5 s was observed in three patients (15%), corresponding to an incidence of 16 ictal asystole events per 100 person-years of monitoring. This is consistent with the rate of 21–32 ictal asystole events per 100 person-years of monitoring observed in the two largest video-EEG series, assuming a mean monitoring duration of 10 days in such studies.

The two latter series also illustrate the complex relation between seizure-triggered cardiac and respiratory dysfunction. Among the 15 patients with ictal asystole, ten had temporal epilepsy and five had extratemporal partial epilepsy. Four of these five patients, but none of those with temporal lobe epilepsy, also showed ictal central apnoea that occurred either before, or concomitant with, the cardiac arrhythmia. Overall, seizure-induced asystole and apnoea might promote each other through cardiorespiratory reflexes or cerebral and brainstem anoxia, but might also indicate a common dysfunction of central autonomic regulation. Whether primary ictal asystole (ie, without prior apnoea or malignant cardiac arrhythmia, such as ventricular fibrillation or torsade de points) can lead to SUDEP remains an open question.

Post-mortem examination
By the common definition, pathological findings in SUDEP exclude any obvious cause of death. However, congestion, thought to indicate neurogenic pulmonary oedema, as well as swelling of other organs, including the brain, is often observed. Subendocardial myocardial vacuolisation, suggestive of chronic heart ischaemia, was also reported in a few SUDEP patients. Finally, an increased expression of heat shock protein-70 was observed in the hippocampal neurons of SUDEP patients, but not in those who had sudden cardiac death, reinforcing the evidence about the most likely mechanisms of SUDEP.

Lessons from sudden unexplained death in non-epilepsy populations
Lessons can be learnt not only in relation to potential application of successful prevention strategies, but also in terms of research into causality from sudden death in other patient groups. Parallels can be drawn in relation to sudden infant death syndrome (SIDS). After many case-control studies, public health campaigns in the UK and many other countries that mainly advocated the supine over the prone position in sleep led to a significant reduction in SIDS rates. The success of this simple measure, which aimed to minimise respiratory compromise, did not preclude others from pursuing the hypothesis that some cases might be due to cardiac arrhythmias of genetic origin. A huge study over the course of 18 years followed 34 442 infants prospectively screened with ECG, with 1-year follow-up available for 33 034 infants. The results, published in 1998, supported the hypothesis, with 12 of 24 SIDS victims having a QTc of greater than 440 ms. Since that study, at least 10% of SIDS cases have been reported to be due to genetic mutations in long QT syndrome genes (eg, KCNQ1) and also in the RYR2 gene, which is implicated in catecholaminergic polymorphic ventricular tachycardia. Experience in this field shows the importance of keeping an open mind with regard to potential mechanisms in SUDEP and their likely heterogeneity, the need for large-scale targeted research to answer specific questions that might alter practice, and the potential success of relatively simple and inexpensive measures in preventing death.

Clinical data show that in the vast majority of cases, SUDEP is triggered by a seizure. Experimental data provide support for both respiratory compromise and cardiac effects, and which of these is the primary event might differ between cases. An individual predisposition for SUDEP is likely to be multifactorial. Although reports of familial cases of SUDEP are rare, a recent observation of two cases in a family with the generalised epilepsy with febrile seizures-plus syndrome and a mutation in the sodium channel gene, the same gene implicated in Dravet syndrome (SCN1A), suggests that in some cases predisposition might be genetically determined. Other epilepsy-related, social, and lifestyle factors could also contribute (figure 2). The additional triggering factors that transform a seizure into a fatal event are also likely to be diverse and include lack of supervision, prone position, and probably others.

Prevention of SUDEP
The ultimate goal of research in this field is to develop methods to prevent SUDEP. Possible strategies include pharmacological and surgical treatment as well as improved supervision of high-risk patients, but strict evidence for their effectiveness is still lacking.

AEDs and avoidance of seizure triggers
As discussed, the largest case-control study to date showed that absence of treatment with AEDs compared with having been on one or two drugs was a strong risk factor. In addition, some controlled studies report non-compliance with AEDs to be a risk factor, suggesting that a maintained stable AED regimen could reduce risk, which would make sense, given the evidence that SUDEP in most cases is a seizure-related event and that poor seizure control is a strong risk factor. We thus believe that stable and effective AED treatment could be important in preventing SUDEP, although direct evidence is lacking. The same applies to avoidance of seizure triggers in those who are susceptible.
Surgery
Several studies compared mortality in patients with and without post-operative seizures after epilepsy surgery, with conflicting results.\textsuperscript{27,34–36} Whereas some found lower SUDEP rates in patients cured by temporal lobe surgery compared with those who continued to have seizures post-operatively,\textsuperscript{34–36} others failed to show such a difference.\textsuperscript{27,37} Other studies compared cohorts of surgically and medically treated patients with drug-resistant epilepsy.\textsuperscript{27,34–40} Three failed to show a difference in mortality between operated and non-operated patients,\textsuperscript{27,34–36} whereas a single series reported a significantly lower death rate in operated patients versus those who were medically treated.\textsuperscript{39} This latter result could be partly explained by differences in the type of epilepsy between the two populations and higher baseline seizure frequency in the non-operated patients.\textsuperscript{39}

In the most recently published study, in which no difference could be detected between surgically and medically treated patients, the latter were more carefully matched to operated patients by age, sex, time of admission in the epilepsy centre, and seizure type.\textsuperscript{87} However, baseline seizure frequency was significantly higher and epilepsy duration was shorter in the surgical group.\textsuperscript{87} Thus, available data do not yet allow firm conclusions to be made about the effect of epilepsy surgery on the risk of SUDEP. One possibility could be that patients who will eventually fail temporal lobe surgery have a so-called temporal-plus epilepsy,\textsuperscript{86,87} involving both the temporal lobe and neighbouring brain regions involved in the central control of cardiorespiratory functions, such as the insula and the frontal operculum, and that this population carries most of the SUDEP burden, both pre-operatively and post-operatively.

Cardiac intervention
As previously discussed, up to 15% of patients with drug-resistant partial epilepsy might develop transient ictal asystole.\textsuperscript{37} This observation raises the issues of whether patients with refractory epilepsy need to be screened for such cardiac arrhythmias, and, if identified, whether these cases would benefit from cardiac intervention. Although it remains unknown whether ictal asystole is always self-limiting or if at times it might lead to SUDEP, most reported cases have so far undergone a permanent pacemaker implantation.\textsuperscript{37} In any event, this procedure seems to be appropriate if ictal asystole is responsible for traumatic falls. One might also speculate about the potential benefit of cardiac intervention in patients in whom ictal asystole complicates seizure-induced central apnoea.

Supervision
A significant proportion of SUDEPs occur in bed and most are unwitnessed. Possible explanations could be that sleep-related seizures differ pathophysio logically or that timely assistance could be protective. Other observations support the latter hypothesis. Kloster and Engelskjon\textsuperscript{97} reported that more SUDEP cases were found prone (71%) than supine (4%). In childhood epilepsy, early mortality is very low, unless there is associated handicap, but more deaths are observed in young adulthood, suggesting the influence of reduced supervision, irregular lifestyle, reduced adherence to treatment, or altered physiology. A trend in support of supervision as protective came from a mortality study in a residential school with special precautions in place at night to enhance supervision of a cohort with special needs and intractable epilepsy.\textsuperscript{99} During the study, deaths occurred with pupils on leave or after they left, but not at the school. Langan’s\textsuperscript{80} case-control study found that a bedroom shared with someone capable of giving assistance and the use of a special monitoring device were both protective. A protective effect of an untrained person suggests that simple measures, such as positioning or stimulating the person and seeking help if needed, can be effective. This should not be taken to imply that all witnessed SUDEP cases are preventable, because there are many documented witnessed deaths. However, it does suggest that there is a reduced risk in the presence of others capable of giving aid. This is difficult to quantify beyond Langan’s data. Nevertheless, there is sufficient evidence in favour of protection from supervision to justify discussing this with patients with uncontrolled epilepsy who seek independent living or who are being encouraged by others to do so.

Keeping patients and relatives informed
There has been much debate, but little evidence, on the advisability or otherwise of discussing risk of death routinely with patients with epilepsy. Those against this position argue that harm, or at the very least, distress, might ensue with no subsequent effect on risk reduction. Their position is that SUDEP is ill understood and cannot be prevented. Some are concerned that a physician might be legally liable in the event of death for not having discussed this issue with the patient, when it might not have been appropriate to do so. They also argue for the patient’s right not to know.\textsuperscript{92} Some hold the view that patients with mild epilepsy are at very low risk, and that such discussions should be reserved for those with severe epilepsy. Others, including patients’ advocates (eg, Epilepsy Bereaved in the UK), believe that patients with epilepsy, as with any other condition, have the right to know the risks associated with their diagnosis. Despite guidance in favour of such information provision by the UK National Institute for Health and Clinical Excellence, a questionnaire survey of UK neurologists showed that only 31% discussed SUDEP with all or most of their patients with epilepsy.\textsuperscript{93} Undoubtedly, more research is needed, but, although individual risk is difficult to estimate, SUDEP is likely to be largely related to generalised tonic-clonic seizures and at least some of these deaths should be preventable.

Epilepsy management involves the patient and the clinician making decisions about treatment and lifestyle that would be aided by a balanced discussion of risks,
which, if well managed, can put such risks into perspective rather than cause alarm. How such discussions are undertaken is outside the scope of this Review, and any advice stated here is supported by experience and not evidence. In practice, discussion of risks associated with seizures is a natural part of the information exchange and is not necessarily difficult. Even at the outset, when discussing the pros and cons of embarking on long-term medical treatment or the importance of avoiding seizure triggers, the rare risk of dying from a seizure, not only from accidental injury or drowning, but also because severe seizures per se can pose a very small risk to life, can be mentioned. General information leaflets on epilepsy should also include reference to the risks associated with epilepsy. More detailed later discussions could follow depending on the individual case. The patient, for example, might seek more specific information about SUDEP. Alternatively, if the patient is considering available options, for example in terms of lifestyle, AED treatment, AED withdrawal, or surgical treatment for epilepsy, the clinician might consider that further information about risks, including SUDEP, would facilitate a more informed choice and a more balanced assessment of the risks and benefits of the course contemplated.

The way forward
The risk of sudden death is clearly increased in the epilepsy population, and SUDEP is the most common seizure-related category. SUDEP is mainly, but not exclusively, a problem for patients with chronic uncontrolled epilepsy. Increased research interest during the past 10–15 years has resulted in substantial advances in our knowledge. The ultimate goal of this development must be to find methods for effective prevention.

To date, case-control studies have mainly identified risk factors linked to chronic poorly controlled epilepsy. We now need to understand what distinguishes people with chronic epilepsy who die suddenly from those who do not. Risks associated with the epilepsy syndrome, unrelated individual predisposition, and factors relating to medical management or lifestyle need to be identified. This could be accomplished in collaborative case-control studies of patients with refractory epilepsy, including epilepsy surgery candidates, for whom a wealth of detailed clinical data are available. More systematic post-mortem studies of SUDEP cases could also be useful to unravel predisposing factors. This could range from detailed neuropathological examinations of critical CNS structures to genetic screening for channelopathies of relevance for cardiac arrhythmias, as has been successfully applied in cardiology and SIDS research. Clinical methods to predict SUDEP risks need to be developed and validated prospectively. This could also be done in large collaborative prospective studies of the high-risk group of surgery candidates.

A better understanding of the mechanisms of SUDEP is essential. An international collaboration between epilepsy surgery centres has recently been launched with the objective of collecting as many cases as possible of SUDEP and near SUDEP that occurred during video-EEG monitoring. This project, MORTEMUS (MORtality in Epilepsy Monitoring Unit Study), is expected to identify 20–30 such cases throughout Europe and to analyse the available video-EEG and ECG data centrally. This study is likely to reveal the extent to which cardiac or respiratory dysfunction, or both, are the primary seizure-induced events that result in SUDEP. Experimental models of SUDEP are also much needed to understand mechanisms and to develop effective interventions.

National monitoring of SUDEP cases could allow broad risk-factor identification if large differences in incidence are identified between regions or countries. Monitoring would also allow assessment of broad intervention strategies and ascertainment of the SUDEP burden, as opposed to relative risk, among different patient groups. Most importantly, we need to develop effective prevention strategies and to be able to assess the interventions already suggested. Validation of the effectiveness of night-time supervision of patients at high risk should be a priority. Further studies on the effectiveness of epilepsy surgery are clearly warranted, not least to better assess the role of potential confounding factors, including preoperative biological differences between excellent and poor surgical candidates. Assessment of the role of AEDs is even more complicated. However, the pooling of data from placebo-controlled clinical trials could be one way forward, and is likely to allow a meaningful comparison of SUDEP rates between treatment with AEDs or placebo (as add-on or monotherapy). Furthermore, the risk of sudden death could be assessed in relation to the indication for the AED treatment.

While admitting the deficiencies in our current knowledge, it seems reasonable to assume that the best way to minimise the risk of SUDEP would be by treatment, pharmacological or surgical, that is effective in controlling seizures and by supervision in appropriate cases. Provision of balanced information to patients and relatives is also of vital importance.

For more on MORTEMUS see http://www.mortemus.org/
Review

Contributors
TT, LN, and PR contributed equally with individual sections to the first draft, which was outlined by TT. TT, LN, and PR jointly revised and finalised the Review.

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