Sudden unexpected death in epilepsy: current knowledge and future directions

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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.

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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[1] 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 unwitnessed 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.[2] 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".[3]

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).[4] 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,[4,5] with incidences ranging from 0·09 to 0·35 per 1000 person-years. However, extrapolating such figures

	Country	Study population	Case ascertainment	Cases (n)	Total person-years	SUDEP incidence (per 1000 person-years)
Ficker and co-workers[4]	USA	Community	Retrospective review of deaths in all epilepsy patients in Rochester (MN)	9	25 940	0·35
Lhatoo and co-workers[5]	UK	Community	Prospective follow-up of newly diagnosed epilepsy cohort	1	11 400	0·09
Jick and co-workers[6]	USA	AED prescription database, age 15–49 years	Retrospective review of deaths	11	8 460	1·3
Tennis and co-workers[7]	Canada	AED prescription database, age 15–49 years	Retrospective review of deaths	18	33 299	0·54
Terrence and co-workers[8]	USA	Community	Retrospective review of autopsy records in medical examiner's office	37	..	0·9
Leestma and co-workers[9]	USA	Community	Retrospective review of autopsy records in medical examiner's office	66	..	1·9
Leestma and co-workers[10]	USA	Community	Prospective ascertainment from medical examiner	60	..	2·3
Langan[11]	Ireland	Community	Retrospective review of autopsy records in coroner's office	15	..	1·5
Opeskin and co-workers[12]	Australia	Community	Prospective ascertainment from coroner's office	50	..	1·3

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

	Country	Study population	Case ascertainment	Cases (n)	Total person-years	SUDEP incidence (per 1000 person-years)
Nilsson and co-workers[13]	Sweden	Epilepsy cohort from hospital discharge register	Retrospective	62	40 508	1·5
Mohanraj and co-workers[14]	UK	Epilepsy clinic, newly diagnosed	Retrospective	7	6482	1·1
Walczak and co-workers[15]	USA	Epilepsy centres	Prospective	20	16 463	1·2
Timmings[16]	UK	Epilepsy clinic	Retrospective	14	7000	2·0
Mohanraj and co-workers[14]	UK	Epilepsy clinic, chronic patients	Retrospective	55	22 935	2·5
Nashef and co-workers[17]	UK	Tertiary referral centre	Retrospective	11	1849	5·9
Vlooswijk and co-workers[18]	Netherlands	Tertiary referral centre	Retrospective	29	..	1·2
Klenerman and co-workers[19]	UK	Residential care, epilepsy	Retrospective	7	3392	2·1
Nashef and co-workers[20]	UK	Residential care, epilepsy and learning disability	Retrospective	14	4135	3·4
McKee and Bodfish[21]	USA	Residential care, epilepsy and mental retardation	Retrospective	11	3012	3·6
Racoosin and co-workers[22]	USA	Refractory epilepsy, AED add-on trials	Prospective	52	9144	3·8
Leestma and co-workers[23]	USA	Refractory epilepsy, lamotrigine add-on trials	Prospective	24	5747	3·5
Derby and co-workers[24]	UK	Refractory epilepsy, >2 AEDs (patients in prescription database)	Retrospective	15	6784	2·2
Annegers and co-workers[25]	International	Refractory epilepsy, vagal nerve stimulation	Retrospective	8	1335	6·0
Dasheiff and co-workers[26]	USA	Epilepsy surgery referrals	Prospective	7	..	9·3
Nilsson and co-workers[27]	Sweden	Surgery candidates not operated	Prospective	4	635	6·3
Sperling and co-workers[28]	USA	Continued seizures after surgery	Prospective	10	1580	6·3

If information on actual number of person-years was not available, incidence was based on an estimate. AED=antiepileptic drug. ..=not available.

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

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]

Thus, SUDEP incidence within the epilepsy population ranges widely, from 0·09 per 1000 person-years in prospective community-based studies of newly diagnosed

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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).[22] 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.[30]

Most of the studies summarised focus on adult patients. Four studies (not shown) specifically assessed SUDEP in children,[31–34] 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.[31] 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).[32] A Swiss hospital-based study identified four cases and estimated the incidence at 0·43 per 1000.[33] 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).[34] 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.[35]

Risk factors identified in controlled studies

Early uncontrolled descriptive studies based on selected populations, often retrospective case series from coroners' records, identified a risk profile for SUDEP that included young age, male sex, poor compliance with AED treatment, and chronic alcohol use.[36] 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

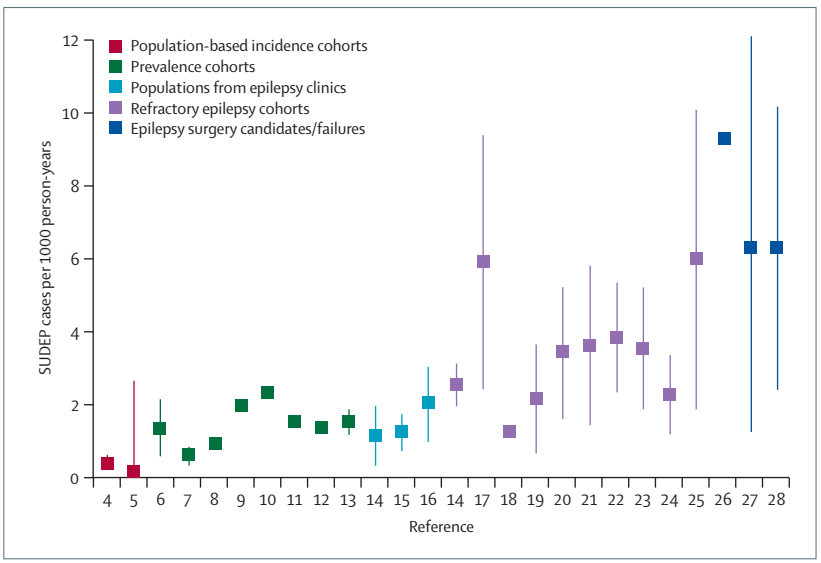

Figure 1: **Incidence of SUDEP in 26 studies of different epilepsy populations**
95% CIs are shown if data were available for their calculation.

circumstances surrounding death.[36] 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).[13,15,21,39,41] One study even reported the risk of SUDEP to be 23 times higher (95% CI 3·2–170) in those who had experienced any seizure during the year of observation compared with seizure-free patients.[13] All three case-control studies that quantified risk by different levels of seizure control found that the risk increased with the frequency of tonic-clonic seizures.[13,15,39]

Absence of treatment with AEDs compared with having been on one or two drugs was a strong risk factor in the largest case-control study (odds ratio [OR] 21·7, 95% CI 4·4–106).[39] However, polytherapy with AEDs was also a risk factor in four of seven studies (table 3).[13,15,21,38] The latter might just be a marker of severe epilepsy, but taking three AEDs concomitantly compared with monotherapy was associated with an OR of 8·1 (2·3–10·0) after adjustment for seizure frequency.[13] With respect to specific AEDs, two studies reported a slightly increased risk with use of carbamazepine.[16,39] An uncontrolled small case series suggested an association between use of lamotrigine in idiopathic epilepsy and SUDEP.[42] Carbamazepine has been shown to reduce heart-rate variability,[43] which in other conditions has been a predictor of an increased risk of sudden death. Lamotrigine has the potential to inhibit the delayed rectifier potassium ion current, a property that has been linked to increased risk of QT prolongation, cardiac arrhythmia, and sudden death for other drug classes.[44] However, lamotrigine use does not seem to result in prolonged QT intervals.[45] Observations of specific

	Design and study population	Cases/controls (n)	Risk factors analysed	Factors that increased risk (comparator)
Jick and co-workers[6]	Retrospective case-control; AED prescription database	11/20	Age at onset*, seizure type*, seizure frequency*, number of AEDs ever taken*, mental retardation*	Mental retardation
Timmings[16]	Retrospective audit of epilepsy clinic	14/1806 (all other patients in the clinic)	Sex, seizure type, seizure frequency, duration of epilepsy, number and type of AEDs	Male sex; idiopathic epilepsy with GTCS; treatment with carbamazepine
Nilsson and co-workers[13]	Retrospective case-control; hospital discharge register	57/171	Epilepsy type, seizure frequency, age at onset/duration, number of AEDs, AED dose changes, other drugs	>2 seizures per year (*vs* 2 or fewer); polytherapy with AEDs; onset of epilepsy <15 years (*vs* >45 years); >2 changes of AED dose per year (*vs* none); use of antipsychotic drugs
Nilsson and co-workers[37]	Retrospective case-control; hospital discharge register	57/171	Use of AED concentration monitoring; AED serum concentrations and their variability; type of AED	Carbamazepine serum concentrations >40 μM (*vs* <40 μM)
McKee and co-workers[21]	Retrospective case-control; residential care for mental retardation	11/?	Sex, age, seizure frequency, number of AEDs, ambulation status, level of mental retardation	Frequent seizures; polytherapy with AEDs; non-ambulatory status
Walczak and co-workers[15]	Prospective case-control; epilepsy centres	20/80	Sex, seizure frequency, duration of epilepsy, number of AEDs, compliance with medication, mental retardation	1–3 GTCSs (*vs* none); duration >30 years (*vs* <15 years); >2 AEDs (*vs* 2 or fewer); IQ <70 (*vs* >79)
Beran and co-workers[38]	Retrospective case-control; epilepsy clinic	21/21	AED polytherapy, handedness, alcohol use, deterioration of epilepsy	Polytherapy (71%) *vs* monotherapy (38%) (p<0·03)
Langan and co-workers[39]	Prospective case-control; multiple sources	154/616	Seizure type, seizure frequency, duration of epilepsy, AED treatment history, psychotropic medication, learning disability, supervision at night	History of GTCSs; frequent GTCSs >10 per 3 months (*vs* <6 per 3 months); >4 AEDs ever used (*vs* <3 AEDs ever); no use of AEDs; current use of carbamazepine; no supervision at night or special precautions (these interventions were protective)
Williams and co-workers[40]	Prospective case-control; SUDEPs on specific AEDs from coroner's office	16/69	Variability of AED medication taking	Greater variability in hair AED concentrations among SUDEP cases *vs* controls
Hitiris and co-workers[41]	Retrospective case-control; epilepsy centre	62/124	Seizure type, seizure frequency, age at onset, AED medication (polytherapy and type of AED)	Seizure within last year (*vs* none); early onset <15 years (*vs* >15 years)

AED=antiepileptic drug. GTCS=generalised tonic-clonic seizure. ?=not known. *Not accounted for in statistical analysis.

***Table 3*: Risk factors for SUDEP in studies that used living patients with epilepsy as controls**

	Design and study population	Cases/controls (n)	Risk factors analysed	Identified risk factors
Leestma and co-workers[23]	Retrospective review of data from lamotrigine trials	20/19	Age, sex, duration of epilepsy, concomitant AEDs, lamotrigine, last dosage and medication duration	Younger age; shorter epilepsy duration *vs* other deaths
George and Davis[46]	Retrospective review; coroner's office	52/44	Post-mortem AED concentrations	Subtherapeutic AED concentrations more prevalent among SUDEPs (69%) than controls (34%)
Kloster and co-workers[47]	Retrospective case-control; tertiary referral centre	42/37	Age, sex, seizure types, seizure frequency, duration of epilepsy, age at epilepsy onset, mental retardation, body position, AED treatment	Young age at onset; primarily generalised seizures; prone body position at death
Schnabel and co-workers[48]	Retrospective case-control; epilepsy residential care	46/108	Age, sex, time of death, geomagnetic activity	Young age
Opeskin and co-workers[49]	Retrospective case-control; coroner's office	44/44	Compliance assessed by post-mortem AED serum concentrations	None
Opeskin and co-workers[12]	Prospective case-control; coroner's office	50/50	Age, sex, type of seizures, type of epilepsy, seizure frequency, duration of epilepsy, mental retardation, AED treatment, psychotropic drugs, medication compliance, place of death	Female sex; death in bed more common in SUDEP; evidence for terminal seizure more common in SUDEP
Vlooswijk and co-workers[18]	Retrospective case-control; tertiary referral centre	29/104	Age, sex, age at onset, duration of epilepsy, seizure types, epilepsy type, seizure frequency, concurrent disorders, mental retardation, AED medication	Younger age at death; earlier epilepsy onset; shorter duration of epilepsy

***Table 4*: Risk factors for SUDEP in studies that used non-SUDEP deaths among patients with epilepsy as controls**

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.[13,15,41] 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 0·1, 95% CI 0·0–0·3), as was sharing a bedroom with someone capable of giving assistance (OR 0·4, 0·2–0·8).[39]

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 analysed in studies that used both types of controls (deceased and living patients with epilepsy). One study reported lower AED concentrations in SUDEP cases than in non-SUDEP

deceased controls,[46] although another study reported no differences.[49] However, post-mortem AED concentrations are unreliable and cannot be compared with ante-mortem concentrations.[50] Whereas one study found greater variability in hair AED concentrations in patients with SUDEP than in living patients with epilepsy,[40] another study found no significant association between SUDEP risk and within-patient variation in AED serum concentrations over time.[37] In summary, controlled studies have mainly identified higher risk with factors linked to chronic uncontrolled epilepsy and suggest that SUDEP in most cases is a seizure-related event.

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.[51–56] 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.[51] One study reported a reduced 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.[52] 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.[53] A second study in tracheostomised sheep noted central apnoea and hypoventilation in all animals.[54] 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.[54] 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.[55]

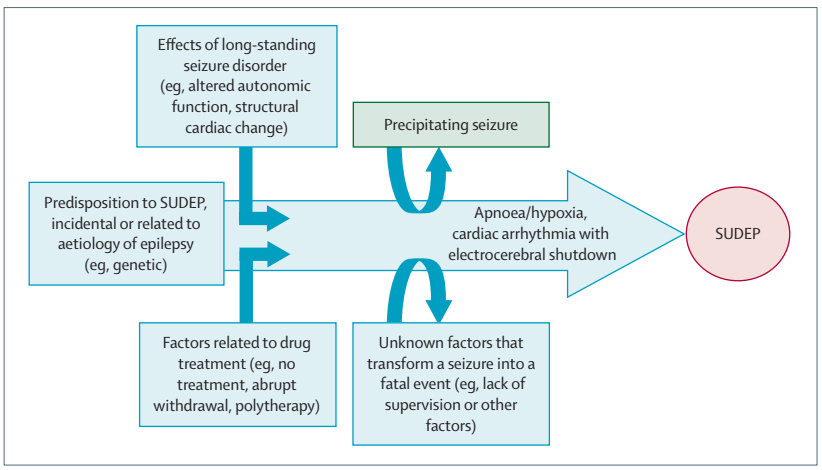

Figure 2: **Interaction between proposed predisposing factors and triggers for SUDEP**

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.[58–60] 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.[57] However, respiration was not monitored in these four patients. In the two monitored cases of near

	Dasheiff and Dickinson[57] (SUDEP*)	Bird and co-workers[58] (SUDEP)	Lee and co-workers[59]† (SUDEP)	So and co-workers[62] (near SUDEP)	McLean and Wimalaratna[60] (SUDEP)	Thomas and co-workers[61] (near SUDEP)
Clinical data						
Sex, age (years)	Male, 48	Male, 47	Female, 41	Female, 20	Female, 50	Male, 18
Age at onset (years)	27	19	Infancy	1	4	14
Relevant history	Myocardial infarction at 38 years, angina	..	..	Recurrent post-ictal respiratory arrest	..	..
Seizure type	CPS	CPS + 2nd GTCS	Partial seizures	CPS + 2nd GTCS	SPS + 2nd GTCS	SPS + CPS
Nocturnal seizure	..	Yes	..	..	..	..
EEG focus	Left temporal	Right temporal	Left temporal	Bi-frontal	..	Right temporal
AEDs at admission	Phenytoin, carbamazepine, phenobarbital	Phenytoin, carbamazepine, gabapentin	Phenobarbital	Valproate, gabapentin, felbamate	Valproate, lamotrigine	..
Monitoring data						
Type of monitoring	Intracranial EEG	Intracranial EEG	Video and scalp EEG	Video and scalp EEG	Ambulatory EEG	Video and scalp EEG
Video	..	Yes	..	Yes	..	Yes
EEG	..	Yes	..	Yes	Yes	Yes
ECG	Yes‡	.. §	.. §	Yes	..	Yes
Respiration	Visual inspection	Visual inspection	..	Visual inspection	..	Visual inspection
Description of event						
Time of event	Day time	Night time	Night time	Day time	Day time	Day time
Cluster of seizures	2 seizures in 1 h	5 seizures in <24 h	No	4 seizures in 6 h	No	7 seizures in 2 h
Type of last seizure	CPS	2nd GTCS	2nd GTCS	2nd GTCS	Unclear	CPS
Primary observation	Ictal or post-ictal cyanosis, cardiorespiratory arrest, immediate resuscitation, ventricular fibrillation on ECG, then terminal asystole	Post-ictal permanent flattening of EEG, right then left, followed by bradycardia for 2 mins, then terminal asystole	Post-ictal EEG slowing followed by marked suppression of EEG, then bradycardia and terminal asystole after 18 mins	Post-ictal central apnoea followed by bradycardia, asystole and EEG flattening after 10 s, 67 s, and 87 s, respectively	Polyspike ictal discharges for 52 s followed by abrupt and terminal flattening of EEG traces	Ictal obstructive apnoea (laryngeal spasm?) followed by bradycardia and asystole after 15 s and 27 s, respectively
Supervision	Yes	No	No	Yes	No	Yes
Resuscitation	Ineffective	Not done	Not done	Effective	Not done	Effective
Post-mortem findings	Marked lung congestion, less relevant findings¶	Mild lung congestion	No abnormality	NA	Mild lung congestion	NA
Interpretation	Cardiac arrythmia	CNS shutdown	CNS shutdown	Central apnoea	CNS shutdown	Obstructive apnoea

Near SUDEP was defined as a cardiorespiratory arrest that resolved after resuscitation. AED=antiepileptic drug. CPS=complex partial seizure. ECG=electrocardiogram. EEG=electroencephalogram. SPS=simple partial seizure. 2nd GTCS=secondarily generalised tonic-clonic seizure. ..=not available. NA=not applicable. *This case, classified as SUDEP by the authors, although clearly seizure related, had pre-existing significant ischaemic heart disease and might therefore not meet the restrictive SUDEP category discussed above. †Abstract only. ‡ECG recording was only started after the onset of the event leading to death. §Pulse artefacts could be observed on EEG recordings. ¶Cardiomegaly, coronary artery stenosis from 0% to 30%, stigma of old myocardial infarction, non-specific hepatitis, thyroid nodule, congestion of liver, spleen and kidneys, calcified arteriovenous malformation in the left temporal lobe, well circumscribed haematoma on the trajectory of the depth electrode.

Table 5: **Clinical characteristics and observations in four patients with SUDEP and two with near SUDEP occurring during monitoring**

SUDEP, apnoea, either central and post-ictal or ictal and obstructive, was thought to be the primary dysfunction that later led to cardiac arrest.[61,62] 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 varies from 7% to 38%.[9–12,39,47,63–67] When witnessed, a seizure, most frequently generalised tonic-clonic, was reported to occur immediately before death in 90% of cases.[68] One study specifically searched for a history of post-ictal breathing difficulties and found confirmative evidence in most cases.[65] 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.[59,70,71]

Ictal bradycardia and sinus arrest have also been described in many case reports.[72] 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

episode recorded.[73–75] 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.[76] 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.[74,75]

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.[74,75] 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 pointes) 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.[63,77] Subendocardial myocardial vacuolisation, suggestive of chronic heart ischaemia, was also reported in a few SUDEP patients.[78] 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 notion that most SUDEP occurs soon after a seizure.[79] None of these pathological findings provide conclusive 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.[80] 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,[81] 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.[82] 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.[83] 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.[39] In addition, some controlled studies report non-compliance with AEDs to be a risk factor,[40,46] 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.[27,84–87] Whereas some found lower SUDEP rates in patients cured by temporal lobe surgery compared with those who continued to have seizures post-operatively,[84–86] others failed to show such a difference.[27,87] Other studies compared cohorts of surgically and medically treated patients with drug-resistant epilepsy.[27,87–89] Three failed to show a difference in mortality between operated and non-operated patients,[27,87,88] whereas a single series reported a significantly lower death rate in operated patients versus those who were medically treated.[89] 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.[89] 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.[87] However, baseline seizure frequency was significantly higher and epilepsy duration was shorter in the surgical group.[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,[90,91] 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.[76] 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.[74,75] 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.

For **Epilepsy Bereaved** see http://www.sudep.org/

Supervision

A significant proportion of SUDEPs occur in bed and most are unwitnessed. Possible explanations could be that sleep-related seizures differ pathophysiologically or that timely assistance could be protective. Other observations support the latter hypothesis. Kloster and Engelskjon[47] 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.[20] During the study, deaths occurred with pupils on leave or after they left, but not at the school. Langan's[39] 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.[38,92] 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.[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,

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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.[94] 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.

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

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 pre-operative 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.

Search strategy and selection criteria

We searched the PubMed database from 1963 to July, 2008, by use of the keyword "epilepsy" combined with "sudden death". 437 articles were identified. Abstracts and relevant articles were reviewed by one of the authors (TT). We also searched lists of references of relevant review articles and book chapters. For the review of SUDEP incidence, we included studies that stated their criteria for SUDEP, number of cases, and real or presumed denominator (person-years). Duplications were excluded if identified. Retrospective or prospective controlled studies on risk factors were included if they provided criteria for SUDEP and epilepsy controls, numbers and information on risk factors analysed, and if cases and controls were selected from the same epilepsy source population.

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.

Conflicts of interest

TT has received research grants or speakers honoraria from Eisai, GlaxoSmithKline, Janssen-Cilag Novartis, Sanofi-Aventis, Pfizer, and UCB. LN has received research grants and speaker or consultancy fees from Eisai, GSK, Janssen-Cilag, Pfizer, and UCB. PR has received speaker or consultancy fees from Eisai, GSK, Janssen-Cilag, Novartis, Sanofi-Aventis, Pfizer, UCB, Valeant, and Cyberonics.

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