Sudden unexpected death in epilepsy

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Sudden unexpected death in epilepsy (SUDEP) refers to the sudden death of a seemingly healthy individual with epilepsy, usually occurring during, or immediately after, a tonic-clonic seizure. The frequency of SUDEP varies depending on the severity of the epilepsy, but overall the risk of sudden death is more than 20 times higher than that in the general population. Several different mechanisms probably exist, and most research has focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction. Data from a pooled analysis of risk factors indicate that the higher the frequency of tonic-clonic seizures, the higher the risk of SUDEP; furthermore, risk of SUDEP is also elevated in male patients, patients with long-duration epilepsy, and those on antiepileptic polytherapy. SUDEP usually occurs when the seizures are not witnessed and often at night. In this Seminar, we provide advice to clinicians on ways to minimise the risk of SUDEP, information to pass on to patients, and medicolegal aspects of these deaths.

Published **Online**
July 6, 2011
DOI:10.1016/S0140-6736(11)60176-1

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Introduction

In recent years, there has been much focus on sudden unexpected death in epilepsy (SUDEP). This term refers to the occurrence of an unexpected death of a seemingly healthy individual with epilepsy, usually in relation to a tonic-clonic seizure, for whom no cause of death can be identified. Although SUDEP has been recognised since the 19th century, only in the past two decades has the full extent and risk of this event been established. SUDEP is a clinical event and not a cause of death, most commonly occurs in the immediate aftermath of convulsive seizures, the pathophysiology of death is uncertain, and, because cases are mostly based on a diagnosis of exclusion, many uncertain cases exist. In this Seminar, we outline the clinical issues, emphasising those that are common in clinical practice, discuss the areas in which there is contemporary research, and review the areas of uncertainty. In parallel to clinical studies, the charity Epilepsy Bereaved has promoted greater public and political recognition of SUDEP, and other epilepsy charities across the world have followed this lead.

Definition

SUDEP has been defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, with exclusion of documented status epilepticus, and when post-mortem examination does not reveal a structural or toxicological cause for death.[1] Accepted practice is to classify all such deaths when there has been an autopsy "definite SUDEP" and those in which there has been no autopsy as "probable SUDEP". This is a broad definition that encompasses heterogeneous cases. Depending on the purpose (eg, for studies on mechanisms of SUDEP), separation of SUDEP cases that occur in seizures and those (much rarer) cases that occur without a seizure might be worthwhile, because the pathophysiology in these groups is probably quite different. Furthermore, in clinical practice, there are many cases that, because information is scarce or because there are plausible explanations for death, are sometimes considered as "possible SUDEP".

Frequency

Results from a US population-based study indicate that the overall rate of sudden unexpected death in people with epilepsy is more than 20 times higher than in the general population.[2] The risk of SUDEP varies by almost a factor of 100, depending on the type of epilepsy population (figure 1). The lowest incidence rates, 0·09 to 0·35 per 1000 person-years, were reported from unselected cohorts of incident cases of epilepsy.[2,4] In general epilepsy populations, incidence rates have ranged from 0·9 to 2·3 per 1000 person-years,[5–14] 1·1 to 5·9 per 1000 person-years in individuals with chronic refractory epilepsy,[15–24] and 6·3 to 9·3 per 1000 person-years in epilepsy surgery candidates or in patients who continue to have seizures after surgery.[25–28] In patients with chronic refractory epilepsy who attend epilepsy referral centres, SUDEP is the leading cause of premature death, accounting for 10–50% of all deaths.[13,19,21–24,29,30]

Risk factors

Risk factors for SUDEP have been analysed in case-control studies of living patients with epilepsy as controls,[5,12,14,31,32] and of patients with epilepsy who have died of other known causes.[11,22,30,33–37] The most informative are the studies that have living patients with epilepsy as controls. However, the few SUDEP cases included in the individual studies has hampered an analysis of any other than the strongest risk factors. To counteract these limitations, the Task Force on Epidemiology of the International League Against Epilepsy (ILAE) pooled data from four major case-control studies of SUDEP[12,14,31,32]

Search strategy and selection criteria

We searched the PubMed database from 1950 to August, 2010, using the terms "epilepsy" and "sudden death" and found 580 articles. We also searched lists of references of relevant review articles and book chapters. We selected articles that we considered to be of greatest importance or interest to this Seminar, with some emphasis on publications from the past 5 years.

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

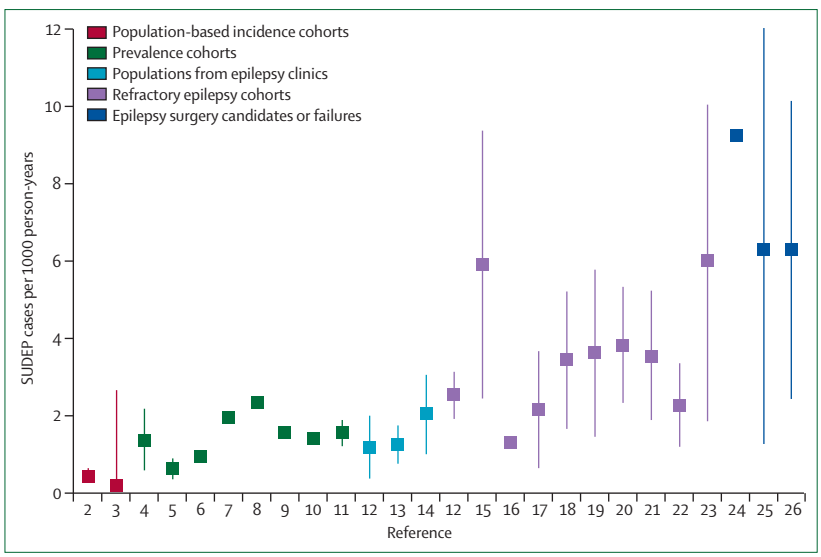

Figure 1: **Incidence rates of SUDEP in 26 studies in different epilepsy populations**
95% CIs are shown where data were available. Reproduced from Tomson and colleagues.[3] SUDEP=sudden unexpected death in epilepsy.

and published its findings (table 1).[38] Case and control definitions and risk factor ascertainment were consistent across the four studies. Risk factors were ascertained through chart review. Altogether, 289 cases and 958 living epilepsy controls were included in this combined analysis.

The risk of SUDEP was 1·4 times higher in male patients than in female patients, 1·7 times higher in those with onset of epilepsy before the age of 16 years than in those with onset between 16 years and 60 years, and twice as high in those who had had epilepsy for longer than 15 years. The most important risk factor was frequency of generalised tonic-clonic seizures (GTCS). Compared with people without GTCS, one to two GTCS per year were associated with an odds ratio of 2·94, three to 12 GTCS per year with an odds ratio of 8·28, and 13–50 GTCS per year with an odds ratio of 9·06. The odds ratio was 14·51 for those with more than 50 GTCS per year.

Patients on combination therapy (polytherapy) with antiepileptic drugs (AEDs) had a three times higher risk of SUDEP than did those on monotherapy. When the frequency of GTCS and AED treatment were studied together in an interaction analysis, both GTCS and polytherapy contributed to a risk of SUDEP, although a high frequency of GTCS had greater risk (table 1).

Pathophysiology

Discussions on the pathophysiology of SUDEP have focused on the final mechanisms by which a seizure could lead to cardiorespiratory arrest and death. However, some of the sudden deaths in people with epilepsy are unrelated to seizures and so SUDEP is probably not a unitary event, and the pathophysiology will vary in different circumstances.

Mechanisms

Most research has focused on the possibility that the primary physiological event is seizure-induced hypoventilation (either central obstructive or both) or a cardiac dysrrhythmia. Other autonomic or central processes have also been studied. Most of the evidence lends support to the predominant role of central hypoventilation, but SUDEP can probably result from different mechanisms in different individuals, and there might be a combination of mechanisms in any one individual.

The experimental studies of death in seizures mainly point to a primary respiratory cause. Classic experiments of death during acute seizures have been done on anaesthetised sheep. In one study,[39] five of 13 sheep died within 5 min of the onset of seizures. The sheep that died also had greater increases in peak left atrial and pulmonary artery pressures and in extravascular lung water than did those that survived, but pulmonary oedema was not severe enough to be the primary cause of death. Although peak aortic pressures and catecholamine concentrations were notably increased during seizures, no differences were recorded between sheep that died and survived. Severe hypoventilation was reported in the animals with seizures that died but not in those that survived (figure 2). The authors concluded that central hypoventilation was the main mechanism of death. In a second study,[40] the increased extravasated pulmonary water was reported to be attributable to changes in pulmonary vascular pressures during seizures. Results from a third study[41] indicated central and obstructive apnoea, without serious arrhythmias. These data conclusively indicated that hypoventilation, of mostly central origin, was the cause of death in most animals. Similarly, in audiogenic mice, death caused by sound-induced seizures was completely prevented by breathing in an oxygen-enriched atmosphere,[42] suggesting that the mechanisms of death are primarily respiratory.

The first clinical study to investigate respiration was done in an electroencephalogram (EEG) telemetry setting, in which respiratory parameters during seizures were measured in 17 patients.[43] Apnoea was recorded in ten of 17 patients and in 20 of 47 seizures, including all three tonic-clonic seizures. The apnoea was central in all patients, but with an obstructive element in three patients. The partial pressure of oxygen (pO_2) concentrations dropped to less than 85% in ten seizures (six patients). Accompanying these changes was an increase in heart rate by an average of 40 beats per min (91% of seizures). A transient self-limiting bradycardia or sinus arrest was documented in four patients, but always in the context of a change in respiratory pattern. Central apnoea, sometimes with added peripheral respiratory obstruction, was concluded to occur in human seizures, with obvious parallels to what was noted in the studies of sheep. In a video-EEG study of localisation-related epilepsy, ictal oxygen desaturation caused by hypoventilation was confirmed to be common, and the extent

www.thelancet.com Published online July 6, 2011 DOI:10.1016/S0140-6736(11)60176-1

of desaturation had a positive correlation with seizure duration[44] and contralateral spread.[45]

Six published cases of SUDEP and three published cases of near-SUDEP have also been recorded in EEG telemetry units and provide the best human evidence of the sequence of events in these deaths.[46–53] All occurred in conjunction with a partial, often secondarily generalised, seizure. A notable finding in five cases was a terminal cessation or diffuse suppression of EEG activity before any cardiac or respiratory changes (CNS shut down). This occurrence reflects profound central inhibition and is possibly an explanation of subsequent central respiratory hypoventilation. Figure 3, from the classic paper of Gastaut and Fischer-Williams,[54] shows that the EEG changes are also different from those seen with cardiac asystole. In four cases, apnoea and hypoventilation were thought to be the primary cause of death; in one other patient with angina and a past history of myocardial infarction, a fatal cardiac arrhythmia was thought to be the main cause. One of the near-SUDEP cases had a pulseless ventricular fibrillation at the end of a secondarily generalised seizure without indications of previous respiratory impairment.[52] The condition reverted after repeated defibrillations.

In none of these cases was there any sophisticated respiratory or cardiac monitoring, but the primary mechanism of death is usually thought to be respiratory (central and obstructive apnoea), although cardiac deaths might also occur and both might be secondary to the profound central inhibition. These findings of ictal hypoventilation have led to the routine use of alarmed pulse-oximetry for all patients in some monitoring units.

The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) is an initiative to collect further cases of SUDEP and near-SUDEP that have occurred during video-EEG monitoring. So far, 13 confirmed SUDEP and three near-SUDEP cases have been identified worldwide and the data are presently being analysed.[55]

In the past few years, there has been a resurgence of interest in the cardiac and autonomic changes that occur in seizures. Ictal asystole is estimated to occur in 0·27–0·40% of patients who have seizures on video-EEG monitoring units.[56,57] Rocamora and colleagues[56] reported the findings in 1244 patients undergoing EEG telemetry. 11 seizures in five patients (0·40%) were associated with asystole of between 4 s and 60 s in duration in complex partial and secondarily generalised seizures with rapid drug reduction. Two of five patients had pre-existing cardiac disease. In a database search of 6825 patients undergoing video-EEG monitoring,[57] ictal asystole was seen in 16 seizures in ten (0·27%) patients; eight patients had had drug reductions. All seizures were complex partial in nature, eight of temporal and two of frontal lobe origin. In the two frontal lobe complex partial seizures, the asystole was thought to have been precipitated by previous respiratory arrest. In the temporal lobe cases, substantial ictal atonia was noted and the authors postulated that drop

	Crude data*		Adjusted data†	
	OR	95% CI	OR	95% CI
All data sources‡				
Sex				
Female	1·00	..	1·00	..
Male	1·30	0·99–1·69	1·42	1·07–1·88
Onset age§				
<16 years	1·85	1·36–2·52	1·72	1·23–2·40
Between 16 years and 60 years	1·00	..	1·00	..
>60 years	0·48	0·11–2·19	0·41	0·08–2·14
Duration of epilepsy¶				
≤15 years	1·00	..	1·00	..
>15 years	1·84	1·39–2·43	1·95	1·45–2·63
Idiopathic cause‖				
No	1·00	..	1·00	..
Yes	0·68	0·49–0·96	0·71	0·50–1·01
Comparisons with polytherapy**				
No AED therapy	1·00	..	1·00	..
Monotherapy	0·89	0·51–1·55	0·74	0·42–1·31
Polytherapy	2·50	1·43–4·38	1·95	1·09–3·47
GTCS frequency per year				
0	1·00	..	1·00	..
1–2	5·10	3·01–8·64	5·07	2·94–8·76
≥3	15·56	10·10–23·97	15·46	9·92–24·10
Unknown	6·12	3·78–9·89	5·35	3·21–8·91
GTCS frequency per year and AED therapy††				
No GTCS and (no therapy or monotherapy)	1·00	..	1·00	..
No GTCS and polytherapy	2·20	0·54–1·22	1·87	0·93–3·75
(1–2 or unknown GTCS) and (no therapy or monotherapy)	4·92	2·73–8·87	4·46	2·43–8·19
(1–2 or unknown GTCS) and polytherapy	10·40	5·69–19·02	9·18	4·96–16·97
≥3 GTCS and (no therapy or monotherapy)	13·90	7·09–27·26	13·49	6·78–26·83
≥3 GTCS and polytherapy	25·20	14·36–44·24	22·64	12·77–40·14
England, Minnesota, and Scotland‡				
Lamotrigine therapy‡‡				
No	1·00	..	1·00	..
Yes	1·91	1·26–2·88	1·86	1·22–2·84
England and Scotland‡				
Lamotrigine therapy and idiopathic generalised epilepsy§§				
No lamotrigine therapy without idiopathic generalised epilepsy	1·00	..	1·00	..
No lamotrigine therapy with idiopathic generalised epilepsy	0·50	0·34–0·74	0·50	0·33–0·74
Lamotrigine therapy without idiopathic generalised epilepsy	1·04	0·57–1·92	1·02	0·55–1·90
Lamotrigine therapy with idiopathic generalised epilepsy	2·20	1·14–4·23	1·85	0·94–3·64

Modified from Hesdorffer and colleagues.[38] OR=odds ratios. SUDEP=sudden unexpected death in epilepsy. ILAE=the International League Against Epilepsy. AED=antiepileptic drug. GTCS=generalised tonic-clonic seizures. *Adjusted for data source. †Adjusted for data source, sex, age at death, and duration of epilepsy. ‡Reference data source is England. §Missing information for ten (3·5%) cases and 35 (3·7%) controls. ¶Missing information for nine (3·1%) cases and 24 (2·5%) controls. ||Missing information for 21 (7·3%) cases and 11 (1·2%) controls. **Missing information for 16 (5·5%) cases and 35 (3·7%) controls. ††Missing information for six (2·7%) cases and four (0·5%) controls. ‡‡Missing information for nine (4·0%) cases and eight (1·0%) controls. §§Missing information for eight (3·4%) cases and two (0·3%) controls.

Table 1: **Risk factors for SUDEP from the ILAE Task Force on Epidemiology pooled analysis from four major case-control studies**

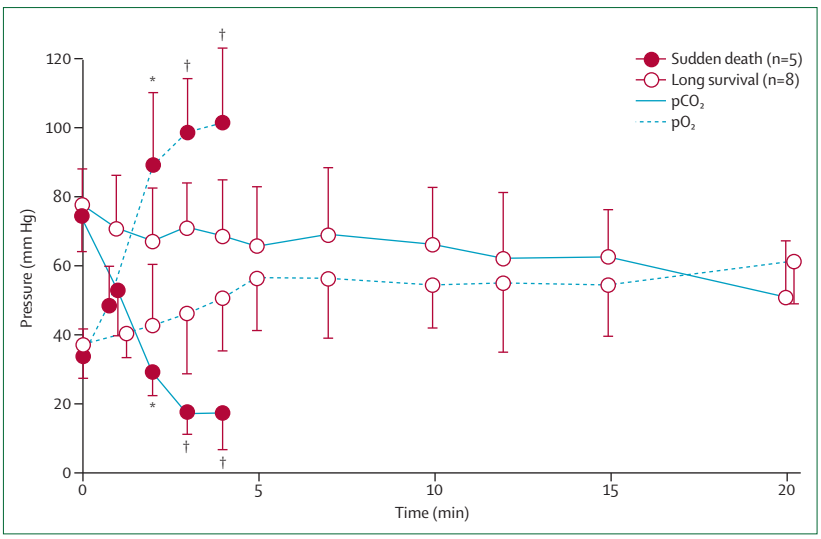

Figure 2: **pO_2 and pCO_2 concentrations during seizures in sheep**
In experimental status epilepticus in sheep, there is a rapid fall in pO_2 and rise in pCO_2 concentrations before death in animals that died (red circles) compared with those that survived (open circles) attributable to hypoventilation. Reproduced from Johnston and colleagues.[39] *p=0·01. †p=0·001. pO_2=partial pressure of oxygen. pCO_2=partial pressure of carbon dioxide. The error bars represent the standard error.

attacks or atonia as a feature of partial seizures could be a clinical warning sign of a risk of asystole. There is one case report of a patient with frequent drop attacks whose seizures dramatically improved with the implantation of a demand pacemaker.[58] Ictal bradyarrhythmia has been recorded in cerebral stimulation and ictal recordings, both clinically and in animals, in the insular, orbital frontal, and anterior temporal lobe regions.[59]

Although serious arrhythmias were rare in these series, the longer-term incidence could be much higher because cardiac changes might occur in only a proportion of a patient's seizures. Implantable loop recorders that permit months of electrocardiographic (ECG) monitoring were used by Rugg-Gunn and colleagues[60] who recorded more than 220 000 patient-hours of ECG in 19 patients. 377 seizures were recorded. Four patients (21%) had bradycardia or periods of asystole with subsequent permanent pacemaker insertion. Three of these four (16% of total) had a period of asystole that was thought to be potentially fatal. Only a few seizures were associated with arrhythmia. In 1977, Schott and colleagues[61] used Holter monitoring and recorded interictal arrhythmia in ten patients (20%).

The insula, anterior cingulate gyrus, and ventromedial prefrontal cortex all affect cardiac rate, rhythm, and output. The hypothalamus controls autonomic responses related to endocrine function (mainly catecholamines) and the amygdala also mediates autonomic responses. Therefore, the fact that epilepsy can affect cardiac function is not surprising. Much interest has focused on heart rate variability, which is reduced in individuals with epilepsy and is mediated through vagal and sympathetic mechanisms.[62–64] Heart rate variability can decrease during seizures and in the immediate aftermath, and this occurrence could be a substrate for cardiac arrhythmia.[65] Furthermore, the extent of the decrease in heart rate variability is associated with the number of seizures and the duration of epilepsy.[65] Similarly, massive changes to epinephrine, norepinephrine, and other hormones occur in seizures, which risk arrhythmia.[65] How important any of these changes are in the mechanisms of SUDEP is unknown. Post-mortem data in SUDEP cases repeatedly indicate mild pulmonary oedema,[9,25,66] but are not thought to be significant enough to cause death and are probably the result of pulmonary vascular rather than neural mechanisms. Minor changes in the heart have been reported, including subendocardial vacuolation suggestive of chronic ischaemia and subtle conduction system abnormalities,[67,68] but these are generally thought not to be severe enough to result in death.

Modulation of the pathophysiology and predisposing factors

Most people with frequent seizures do not die in SUDEP; therefore, an individual susceptibility exists. Furthermore, in most cases, even the predisposed individual will usually have had many non-fatal seizures before the final fatal one, which suggests that there are modulating factors that establish whether the course of the seizure will be benign or will lead up to SUDEP. Various aspects have been studied but a satisfactory unitary explanation of the mechanisms of SUDEP remains elusive.

The emerging profile of the susceptible individual is someone who has long-standing epilepsy with an onset at young age and frequent tonic-clonic seizures.[38] This association might be explained simply by the extended exposure to increasing numbers of potentially fatal seizures. However, chronic refractory epilepsy might lead to subtle myocardial changes[67,68] or impairment of autonomic cardiac control[62,63,65,69] thus increasing the susceptibility to SUDEP. In a small case-control study, however, no differences in interictal heart rate variability were reported in seven patients who later died in SUDEP versus seven patients with epilepsy who did not die.[70]

Interest has also focused on prolonged QT syndromes. Seizures themselves can prolong the QT interval directly, especially if seizure discharges involve the insular region,[71] hypercapnia[72] and hypoxia,[73] and catecholamine release.[74] Genetic long QT syndromes are associated with sudden death because of the risk of torsade de pointes arrhythmia. These genetic disorders are channelopathies, as are some of the epilepsies. Some channelopathies might underpin epilepsy and prolong QT, which might contribute to SUDEP, as supported by the co-occurrence of epilepsy in a mouse model of human long QT mutations.[75] Hindocha and colleagues[76] reported data on a family with epilepsy and an *SCN1A* mutation, for whom SUDEP occurred in two members (not genotyped). Eight genes caused a long QT syndrome (including *SCN5A, KCNQ1, KCNH2, KCNE1,* and *KCNE2*). Mutations in *SCN5A* or *KCNH2*

genes were recently reported in six of 68 other SUDEP cases.[77] In knock-out mice, one group has indicated that *KCNQ* is a candidate susceptibility gene to SUDEP.[78]

Lhatoo and colleagues[79] have suggested that prolonged postictal EEG suppression might indicate an increased susceptibility. Postictal flattening of the EEG after a convulsive seizure recorded during epilepsy monitoring was significantly longer in ten SUDEP cases than in 30 epilepsy controls. This prolonged cerebral inhibition might be the mechanism of postictal respiratory dysfunction.

The pharmacological treatment might also be relevant as a predisposing or modulating factor (see below), although SUDEP has been recorded before modern treatment was available.

Case-control studies[12,14,30–32] and direct observations of SUDEP and near-SUDEP cases provide clues to factors that might modulate the effects of a potentially lethal seizure. Absence of supervision was identified as an important risk factor in one case-control study,[31] and other observations discussed below provide indirect evidence that interaction with patients immediately after a convulsive seizure might prevent SUDEP.

Circumstances in which SUDEP occurs

Most cases of SUDEP are unwitnessed, occurring in seizures in which the individual is unobserved and in which assistance is therefore not at hand. Many occur during sleep, and usually when the individual is sleeping alone. Nashef and colleagues[80] interviewed the relatives of 26 cases of SUDEP. In 24 of 26 cases, the death was unwitnessed and evidence indicative of a seizure was reported in most patients. In the case-control study of SUDEP by Langan and colleagues,[31] supervision was confirmed as a protective factor independent of seizure control. In a study[19] of SUDEP in a residential school for children with epilepsy who were closely supervised at night, a low incidence of SUDEP was reported and no witnessed deaths occurred during term time. There were greater risks when the children were at home in the holidays without the same intense night-time surveillance.[19] In an investigation from Norway[30] 42 patients with definite SUDEP were reported, 25 of whom died during sleep; of the 24 cases in whom position was recorded, 17 were found dead in the prone position. There were positive signs of a seizure in 67% of the SUDEP cases.

Nashef and colleagues[80] postulated that an accompanying individual could stimulate (eg, by shaking) an individual whose breathing had ceased, during or after a convulsive seizure, and that this stimulation restores normal cardiorespiratory function. In our opinion, this supposition is plausible and might be particularly important in seizures occurring in sleep.

Few definite SUDEP cases have been witnessed. 80% of the 15 cases reported by Langan and colleagues[81] had a seizure immediately before death and nine of 12 cases reported by Kloster and colleagues.[30] In all witnessed deaths, seizures stopped before death. Respiratory arrest (obstructive or central) is thought to be the cause of death in most witnessed cases.

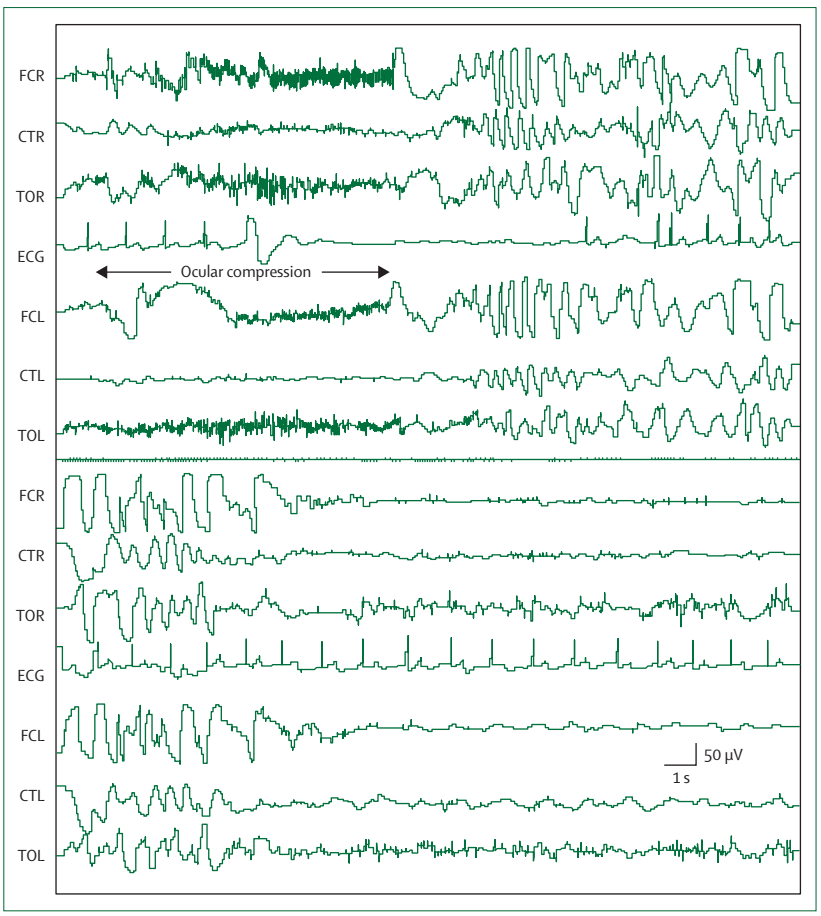

Figure 3: **EEG effects of asystole in a case of syncope produced by ocular compression**
There was asystole for 10 s and the EEG showed generalised slow activity (theta and delta), which rapidly reversed when the heart began beating again (the lower trace is a continuation of the upper one). Reproduced from Gastaut and Fischer-Williams.[54] EEG=electroencephalogram. FCR=frontal-central right. CTR=central-temporal right. TOR=temporal-occipital right. ECG=electrocardiogram. FCL=frontal-central left. CTL=central-temporal left. TOL=temporal-occipital left.

Association with frequency of seizures

In almost all studies, the risk of SUDEP is concluded to be high in patients who have a high number of tonic-clonic seizures; thus there is a positive association with seizure frequency and the duration of epilepsy.[12,14,31,38] Nilsson and colleagues[12] were one of the first to report this link, and showed that, when compared with patients with up to two seizures in the previous year, the relative risk of SUDEP was 7·21 in those with a history of three to 12 seizures, 8·64 in those with 13–50 seizures, and 10·16 in those with a history of more than 50 seizures in the previous year. The overall relative risk in patients with seizures in the previous year was 23·20 compared with those who were seizure free. The findings were mainly confirmed in the combined analysis of four case-control studies.[38]

Although SUDEP is more common in patients with chronic severe epilepsy, SUDEP can also occur in patients with infrequent seizures or even in the first epileptic seizure. SUDEP can occur in patients with occasional tonic-clonic seizures in idiopathic generalised epilepsy, and, furthermore, lamotrigine was suggested to have an increased risk with this form of epilepsy in the combined analysis of the ILAE Task Force.[38]

There are sporadic reports of photic-induced seizures that resulted in death, and anxiety has focused on cartoon-induced and video game-induced seizures after events on Dec 16, 1997, when nearly 700 children were admitted to hospitals because of seizures induced by watching the cartoon Pokémon. In this cartoon, there was a 4-s rocket launch with whole-screen red and blue fields flashing at a 12·5 Hz-induced photosensitivity per s.[82] Some cases were probably caused by mass hysteria, but definite seizures also occurred, and press reports of deaths were widely circulated.

Can risk of SUDEP be modified by intervention?

AEDs

Whether drugs affect the risk of SUDEP, and whether judicious treatment lowers this risk, is important to know. However, the association between AEDs and SUDEP is complex and findings on this issue are partly contradictory.

Because SUDEP usually seems to be associated with the occurrence of a generalised convulsive seizure, and a high frequency of GTCS is the most important risk factor, the assumption that effective drug treatment would reduce the incidence of SUDEP is reasonable. The conclusion from one case-control study was that the absence of treatment increased the risk of SUDEP by 21·7 times compared with those taking one to two AEDs.[31] In the ILAE Task Force pooled analysis, AED monotherapy tended to be protective compared with no treatment, but this tendency was not significant.[38] One of the studies[12] included in the pooled analysis excluded untreated patients.

In further support of the protective effect of AED treatment, poor compliance with treatment might have increased the risk of SUDEP.[83,84] Non-adherence is associated with poor seizure control.[85] Faught and colleagues[86] used Medicaid claims data to evaluate adherence to treatment in more than 33 000 patients with AED prescriptions. Periods of non-adherence were associated with a more than three times increase in mortality compared with adherence (hazard ratio 3·32). However, these investigators included all causes of death, but SUDEP probably contributed to the increased mortality.

Attempts have been made to use post-mortem AED blood concentrations to assess the level of compliance in SUDEP cases, but there are conflicting results.[3] Williams and collaborators[87] measured AED concentrations in hair segments (1 cm assumed to be indicative of 1 month). The coefficient of variation of the corrected mean hair concentration was used as an index of variability of an individual's AED compliance. The observed variability of hair concentrations was greater in SUDEP cases than in epilepsy outpatients or inpatients, suggesting more variable AED ingestion over time in these patients.

Unstable AED treatment, with frequent changes in the prescribed dose might increase the risk of SUDEP. In one case-control study, a relative risk of 6·08 was reported in patients with three to five changes per year compared with those with unchanged dosages.[12] However, given that frequent drug changes are more likely to be made in patients who have frequent seizures than in other patients with epilepsy, these drug changes cannot be concluded to cause SUDEP. This point is important when counselling relatives and in some medicolegal settings.

Although effective AED treatment is likely to be protective, AEDs in some circumstances might increase the risk of SUDEP. Some epilepsy drugs have potential effects on cardiac conduction through their membrane-stabilising effects and their effects on autonomic function. Attention has mostly focused on the sodium-channel-blocking drugs such as carbamazepine and lamotrigine. Timmings[15] reported that a disproportionate number of SUDEP cases in one unit were taking carbamazepine, and that this drug-induced lengthening of the ECG QT interval or reduction of heart rate variability,[88,89] combined with a mild pro-arrhythmic effect of epileptic seizure discharges, might lead to fatal arrhythmia. In some case-control studies, an increased risk has been reported with carbamazepine[31] or in association with high plasma concentrations of the drug.[90] These associations were, however, not confirmed in the ILAE Task Force pooled analysis, which included these two case-control studies.[38]

Data from one uncontrolled small case-series[91] suggested an association between lamotrigine in patients with idiopathic epilepsy and SUDEP. Similarly, the ILAE Task Force pooled analysis also reported a slight but significantly increased risk for SUDEP with lamotrigine in patients with idiopathic generalised epilepsy.[38] Whether these links are spurious associations, perhaps reflecting treatment preferences in different time periods, or whether there might be a causal relationship, remains to be clarified. Observations of risk of SUDEP with these two or other specific AEDs have not been confirmed in other studies. At present, there is no reason to advise against the use of any specific AED to reduce the risk of SUDEP.

Polytherapy with AEDs had an associated increased risk of SUDEP in several case-control studies[12,14,20,92] and in the ILAE Task Force combined analysis.[38] Association is not necessarily causal, and polytherapy might simply be a marker of severe epilepsy. Ryvlin and colleagues[93] analysed the risk of SUDEP in 101 randomised placebo-controlled add-on trials of AEDs in patients with drug-resistant partial seizures. The risk of SUDEP was reduced by almost 80% in patients randomly assigned to active AED add-on treatment compared with those on placebo (odds ratio 0·21; 95% CI 0·07–0·67). Under these circumstances, adding one more AED to the

www.thelancet.com Published online July 6, 2011 DOI:10.1016/S0140-6736(11)60176-1

existing treatment seemed to protect against SUDEP rather than to increase the risk. The likely explanation is that adding the active drug improved seizure control more than did adding placebo, and the data indicate the importance of giving priority to achieving seizure control in epilepsy treatment.

Other prescribed drugs

The risk of SUDEP could also potentially be affected by prescribed drugs other than AEDs. Some antipsychotics and other drugs that act on the cardiac delayed rectifier potassium ion current (*I*kr) or that otherwise prolong the QT interval can be pro-arrhythmic and have been associated with sudden cardiac death.[94] Whether such pharmacological properties are relevant for SUDEP, or indeed whether drugs used to prevent sudden cardiac death[95] could protect against SUDEP is unknown. In one case-control study, a modest increase in risk of SUDEP with concomitant use of antipsychotics or anxiolytics was reported,[12] but this finding has not been replicated in other studies.

Based on data from a mice model, treatment with antidepressants of the selective serotonin-reuptake inhibitor type could reduce the risk of SUDEP by prevention of postictal respiratory arrest.[96] Bateman and colleagues[97] reviewed data from patients with refractory partial epilepsy undergoing video-EEG monitoring, and concluded that ictal oxygen desaturation was significantly less frequent in patients treated with selective serotonin-reuptake inhibitors. However, the effects of selective serotonin-reuptake inhibitors, β blockers, or statins in the prevention of SUDEP have not yet been assessed.

Epilepsy surgery

Successful epilepsy surgery has the potential to cure epilepsy and render a patient with previous refractory epilepsy seizure-free. Thus, surgery can probably reduce the risk of SUDEP. Table 2 summarises the data from five studies that assessed the incidence rates of SUDEP after surgery. The rates in patients who have undergone epilepsy surgery range from 1·8 to 4·0 per 1000 patient-years,[26,28,98–100] which seems to be lower than that in surgery candidates with refractory epilepsy (figure 1).

The risk of SUDEP after surgery apparently depends on the outcome in terms of seizure control. In a surgery series from Philadelphia, PA, USA, ten SUDEPs were reported in 583 patients, and no cases were reported in the 256 patients who were seizure free since surgery.[101] Similarly, none of the six SUDEP cases were seizure free in the follow-up of 596 patients in the population-based Swedish Epilepsy Surgery Registry.[26] In a series from Indiana, IN, USA, two SUDEPs in 41 patients who continued to have seizures after surgery were reported compared with one of 171 seizure-free patients.[102] In a series from the National Hospital for Neurology and Neurosurgery in the UK, all five reported SUDEPs occurred in patients whose seizures were not fully controlled after surgery. There was no SUDEP among the 209 patients who were completely seizure free since surgery.[100] The Cleveland Clinic Epilepsy Centre, OH, USA, identified seven SUDEPs in patients who had undergone epilepsy surgery; none was seizure free at the time of death.[103] Although these data are intriguing, the observations cannot be regarded as firm evidence for the effectiveness of epilepsy surgery in reducing the risk of SUDEP because there might be intrinsic differences in medical aspects and in therapy between patients with favourable and unfavourable seizure outcomes of surgery.[69]

Vagal nerve stimulation

Repeated concern has been expressed about the potential of vagal nerve stimulation to induce bradycardia or cardiac arrest. Information from case reports has shown this risk to be a real possibility.[104] Because of this risk, an intraoperative lead test is done during insertion of the device,[105] and bradycardia or asystole is induced in occasional patients. In one report of three cases with bradycardia during insertion, no problems in subsequent chronic therapy were reported,[106] but if bradycardia is induced during insertion, great caution should be applied. However, in a review of a cohort of 1819 individuals (partly funded by the manufacturers of the device), with a total of 3176·3 person-years from implantation, only 25 deaths were reported and the authors felt that this finding was no higher than rates reported in other chronic epilepsy populations.[24] Obstructive sleep apnoea is also common in patients with epilepsy,[107] and there is evidence indicating that vagal nerve stimulation can exacerbate this tendency.[108]

Cardiac pacing as a preventive measure

Cardiac monitoring of patients with chronic epilepsy has indicated that many patients have ictal bradycardia. In one study of 19 patients with severe intractable focal epilepsy, severe ictal bradycardia was recorded in 2% of seizures and four patients had periods of bradycardia or asystole of a severity, which was considered sufficient to warrant cardiac pacemaker implantation.[60] Whether these cardiac abnormalities would increase the risk of SUDEP is not known, and the extent to which ictal bradycardia or asystole is a benign self-limiting

	Type of cohort	n	Incidence of SUDEP
Hennessy et al[28]	Temporal lobe epilepsy, single centre, UK	299	2·2 per 1000 patient-years
Sperling et al[98]	Any epilepsy surgery, single centre, USA	393	4·0 per 1000 patient-years
Salanova et al[99]	Temporal lobe epilepsy, single centre, USA	215	4·0 per 1000 patient-years*
Nilsson et al[26]	Any epilepsy surgery, population-based Sweden	563	2·4 per 1000 patient-years
Bell et al[100]	Any epilepsy surgery, single centre, UK	469	1·8 per 1000 patient-years†

SUDEP=sudden unexpected death in epilepsy. *Includes three patients "who died during seizures" and three who died "suddenly and for unexplained reasons". †In addition to five SUDEPs, two were other seizure-related deaths.

Table 2: **SUDEP incidence rates after epilepsy surgery**

***Panel:* Measures in clinical practice to reduce the risk of SUDEP**

- Reduction of tonic-clonic seizures: optimum treatment, good drug compliance, lifestyle advice (eg, alcohol intake, sleep deprivation)
- Treatment changes: change in a gradual staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patients should have access to immediate advice in the event of worsening seizures during periods of change
- Supervision at night for patients at high risk: attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring)
- Choice of drugs: caution with antiepileptic drugs with potential cardiorespiratory adverse effects
- Act on ictal warning signs: tonic-clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnoea, and post-ictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with pre-existing cardiac or respiratory impairment
- Supervision after a tonic-clonic seizure: continuous attendance until full consciousness is restored; call emergency services for high-risk seizures
- Counselling on the risks: lifestyle and treatment decisions are the patient's prerogative and the physician's role is to provide a risk versus benefit analysis

SUDEP=sudden unexpected death in epilepsy. EEG=electroencephalogram.

arrhythmia or a relevant mechanism for SUDEP is being debated.[109,110] Nevertheless, in patients with evidence of marked cardiac arrhythmia associated with seizures, the possibility that this condition has a risk would be sufficient in many cases to recommend on-demand cardiac pacing, which has been common practice.[57,58,111]

Another issue relates to patients who have a sudden loss of tone in the course of a complex partial seizure (causing a 'drop attack'). Such sudden loss of tone is an unusual feature of epilepsy but is common in ictal asystole, and it has been suggested that this clinical sign is indicative of ictal asystole and so should prompt cardiac monitoring.[57,58]

Advice to clinicians managing patients with epilepsy

The panel lists some potential ways in which a clinician can minimise the occurrence of SUDEP. Because there are no data on the effectiveness of any particular clinical strategy, these suggestions are only speculative. However, on the basis of the evidence we have discussed, reducing the occurrence of tonic-clonic seizures, exercising caution in changing antiepileptic drugs, and improving post-ictal surveillance are likely to be beneficial.

Information to patients

In general, patients should be fully informed about the risks of any condition or its treatment, although there is debate about the quality and timing of information about SUDEP to patients and relatives. Bereaved relatives often complain that they were uninformed of the risks.

Full discussion of the risk with patients and relatives is often recommended, but, because of the infrequency of SUDEP (figure 1) and the absence of predictive or preventive measures, some clinicians believe that a policy of informing all patients will cause stress and anxiety. Many patients excessively dwell on the risk, which can impair confidence and quality of life. Furthermore, stress might increase the likelihood of SUDEP.[112,113] Others have argued that information on SUDEP should only be given to high-risk patients.[114,115]

In a survey of British neurologists, only 4·7% discussed SUDEP with all their patients with epilepsy, 25·6% with most patients, 61·2% with a few of their patients, and 7·5% with none of their patients.[116] Practice here was not in accordance with guidelines, but the authors point out that this finding "reflects what every doctor knows: that patients differ vastly in their need for information". Another debate concerns when to tell patients. At a recent ILAE meeting in the UK, the motion that all patients should be told about SUDEP at the time of the first appointment was voted down. Representatives from epilepsy charities take a different view, and believe that awareness that epilepsy can kill is paramount. We believe that most patients should have information about SUDEP, because although epilepsy is not usually a life-threatening condition, a small number of people do die in epileptic seizures from accidents and SUDEP, and the risk can be minimised by controlling tonic-clonic seizures. This information is best provided as part of comprehensive counselling about risks and prevention. Putting the risks in perspective is sometimes helpful—for example, comparing the risk of SUDEP (10–35 in 100 000 person-years) with the similar yearly risks of accidental death in a motor accident (about 18 in 100 000 cars or 55 per 100 000 motorcycles).[117]

Medicolegal considerations and future recommendations

In coronial and legal practice, several difficult issues have arisen in relation to various aspects of SUDEP. The first issue regards the use of the term SUDEP. Although allowable as a term for use in death certification in many countries, SUDEP is actually not a cause of death, but is a description of a clinical scenario. There might be many factors leading up to the occurrence of SUDEP, some inherent and some related to the quality of clinical care.

Second, there are difficulties attributing poor clinical care as a cause of SUDEP. Some aspect of poor clinical care is often loosely claimed to be responsible for SUDEP. Such claims are often not possible to prove from a legal point of view. Furthermore, there are no data to indicate that any clinical strategy will prevent SUDEP; therefore, direct evidence of the benefits of any particular aspect of care is needed. The risk of SUDEP in any individual with tonic-clonic seizure is low and this is an important consideration in some medicolegal situations in which the risks of a clinical decision are being weighed.

Third, the differentiation of SUDEP from drug-induced respiratory depression can be a source of contention. There is no consensus on how to distinguish SUDEP from drug-induced respiratory depression (ie, from the

www.thelancet.com Published online July 6, 2011 DOI:10.1016/S0140-6736(11)60176-1

emergency treatment of a seizure). Respiratory depression is more common after a seizure than after acute treatment (eg, with benzodiazepines),[118] but can occur in both cases.

Fourth, clarity is needed about how long after a seizure a death can be attributed to SUDEP. In cases of SUDEP that are argued to be seizure related, the question might arise about the elapsed time and how long after any particular seizure SUDEP can be considered to have occurred. In the definition of SUDEP by Nashef,[1] death occurs within minutes or hours of the final ictus (unless life is prolonged artificially by resuscitation). However, it is difficult to understand how a cardiac or respiratory mechanism, directly attributable to a seizure, could be operative hours after the seizure. It would be helpful to have clearer definitions of how much elapsed time after the seizure is allowable. This issue is also relevant when establishing whether respiratory depression is drug-induced or seizure-induced.

Fifth, in some cases, issues have arisen about the adequacy of care after a tonic-clonic seizure. In our opinion, a failure of medical or nursing staff to maintain a close observation of a patient after a tonic-clonic seizure, until full consciousness is recovered, is potentially negligent practice. In a hospital setting, all patients need to be attended in the aftermath of the seizure until consciousness is regained so that impending respiratory or cardiac complications can be immediately treated.

Sixth, arguments have arisen about the level of information provision to patients or families about the risks of SUDEP. Beran[114] believes that because a discussion of SUDEP is unlikely to lead to a change in a patient's decision on treatment, the failure to discuss the risks of SUDEP is not likely to amount to negligence. Beran goes further and states that, if discussion of this topic adversely affects quality of life, the information might provide grounds for negligence, although this scenario seems unlikely to us. The general opinion, in the UK at least, is that individuals should be warned of the risk but, as discussed above, controversy exists about whether all patients (including those at low risk) should be warned or at what stage in their epilepsy.

Consistency in death certification of SUDEP cases is important for medicolegal reasons and for research purposes. Unfortunately, SUDEP is not uniformly acknowledged among all pathologists,[119] which severely hampers the possibility of estimating the incidence of SUDEP in different regions, monitoring time trends, and assessing the effectiveness of intervention strategies. Autopsies of patients with SUDEP should include a neuropathological examination with documentation of any brain pathological changes underlying the epilepsy, toxicology, and examination of the heart, lungs, and other organs to exclude alternative pathological changes.[120] Use of standardised autopsy protocols in all suspected SUDEP cases would be a major advancement.

Contributors

Both authors contributed equally to the design, research, and writing of this Seminar.

Conflicts of interest:

SS has received consultancy fees from Janssen Cilag, UCB Pharma, and Eisai, and has received speaker's honoraria from GlaxoSmithKline, Janssen Cilag, and UCB Pharma. TT has received research grants from Eisai, GlaxoSmithKline, Janssen-Cilag Novartis, Sanofi-Aventis, Pfizer, and UCB Pharma. He has received speaker's honoraria from UCB Pharma and Eisai, and has received travel expenses from UCB Pharma.

Acknowledgments

The contribution by SS was partly undertaken at University College London Hospital, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres' funding scheme.

References

1 Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia* 1997; **38** (suppl 11): S6–S8.

2 Ficker DM, So EL, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology* 1998; **51:** 1270–74.

3 Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 2008; **7:** 1021–31.

4 Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol* 2001; **49:** 336–44.

5 Jick SS, Cole TB, Mesher RA, Tennis P, Jick H. Sudden unexpected death in young persons with primary epilepsy. *Pharmacoepidemiol Drug Safety* 1992; **1:** 59–64.

6 Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. *Epilepsia* 1995; **36:** 29–36.

7 Terrence CF Jr, Wisotzkey HM, Perper JA. Unexpected, unexplained death in epileptic patients. *Neurology* 1975; **25:** 594–98.

8 Leestma JE, Kalelkar MB, Teas SS, Jay GW, Hughes JR. Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia* 1984; **25:** 84–88.

9 Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. *Ann Neurol* 1989; **26:** 195–203.

10 Langan Y. The incidence of sudden unexpected deaths in epilepsy in South Dublin and Wicklow. *Seizure* 1998; **7:** 355–58.

11 Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure* 2003; **12:** 456–64.

12 Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999; **353:** 888–93.

13 Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. *Lancet Neurol* 2006; **5:** 481–87.

14 Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001; **56:** 519–25.

15 Timmings PL. Sudden unexpected death in epilepsy: a local audit. *Seizure* 1993; **2:** 287–90.

16 Nashef L, Sander JWAS, Fish DR, Shorvon SD. Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral center. *J Neurol Neurosurg Psychiatry* 1995; **58:** 462–64.

17 Vlooswijk MC, Majoie HJ, De Krom MC, Tan IY, Aldenkamp AP. SUDEP in the Netherlands: a retrospective study in a tertiary referral center. *Seizure* 2007; **16:** 153–59.

18 Klenerman P, Sander JWAS, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long term residential care. *J Neurol Neurosurg Psychiatry* 1993; **56:** 149–52.

19 Nashef L, Fish DR, Garner S, Sander JWAS, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 1995; **36:** 1187–94.

20 McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. *Am J Ment Retard* 2000; **105:** 229–35.

21 Racoosin JA, Feeney J, Burkhart G, Boehm G. Mortality in antiepileptic drug development programs. *Neurology* 2001; **56:** 514–19.

22 Leestma JE, Annegers IF, Brodie MI, Brown S, Schraeder P, Siscovick D. Sudden unexplained death in epilepsy: observations from a large clinical development program. *Epilepsia* 1997; **38:** 47–55.

23 Derby LE, Tennis P, Jick H. Sudden unexpected death among subjects with refractory epilepsy. *Epilepsia* 1996; **37:** 931–35.

24 Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia* 2000; **41:** 549–53.

25 Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 1991; **8:** 216–22.

26 Nilsson L, Ahlbom A, Farahmand BY, Tomson T. Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia* 2003; **44:** 575–81.

27 Sperling MR, Harris A, Nei M, Liporice JD, O'Connor MJ. Mortality after epilepsy surgery. *Epilepsia* 2005; **46** (suppl 11): 49–53.

28 Hennessy MJ, Langan Y, Elwes RD, et al. A study of mortality after temporal lobe epilepsy surgery. *Neurology* 1999; **53:** 1276–83.

29 Lip GYH, Brodie MJ. Sudden death in epilepsy: an avoidable outcome? *J R Soc Med* 1992; **85:** 609–11.

30 Kloster R, Engelskjon T. Sudden unexpected death in epilepsy: a clinical perspective and a search for risk factors. *J Neurol Neurosurg Psychiatry* 1999; **67:** 439–44.

31 Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005; **64:** 1131–33.

32 Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. *Epilepsy Behav* 2007; **10:** 138–41.

33 Birnbach CD, Wilensky AJ, Dodrill CB. Predictors of early mortality and sudden death in epilepsy: a multidisciplinary approach. *J Epilepsy* 1991; **4:** 11–17.

34 George JR, Davis GG. Comparison of anti-epileptic drug levels in different cases of sudden death. *J Forensic Sci* 1998; **43:** 598–603.

35 Schnabel R, Beblo M, May TW. Is geomagnetic activity a risk factor for sudden unexplained death in epilepsies? *Neurology* 2000; **54:** 903–08.

36 Opeskin K, Harvey AS, Cordner SM, Berkovic SF. Sudden unexpected death in epilepsy in Victoria. *J Clin Neurosci* 2000; **7:** 34–37.

37 Shields LB, Hunsaker DM, Husaker III JC, Parker Jr JC. Sudden unexpected death in epilepsy: neuropathological findings. *Am J Forensic Med Pathol* 2002; **23:** 307–10.

38 Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. *Epilepsia* 2011; published online Jan 28. DOI:10.1111/j.1528-1167.2010.02952.x.

39 Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death. *Ann Neurol* 1995; **37:** 531–37.

40 Johnston SC, Darragh TM, Simon RP. Posticatal pulmonary edema requires pulmonary vascular pressure increases. *Epilepsia* 1996; **37:** 428–32.

41 Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. *Ann Neurol* 1997; **42:** 588–94.

42 Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. *Epilepsia* 2004; **45:** 993–96.

43 Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry* 1996; **60:** 297–300.

44 Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain* 2008; **131:** 3239–45.

45 Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures: intracranial EEG recordings in refractory temporal lobe epilepsy. *Epilepsia* 2009; **50:** 2557–62.

46 Dasheiff RM, Dickinson LJ. Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure. *Arch Neurol* 1986; **43:** 194–96.

47 Bird JM, Dembny AT, Sandeman D, Butler S. Sudden unexplained death in epilepsy: an intracranially monitored case. *Epilepsia* 1997; **38** (suppl 11): S52–56.

48 Lee HW, Hong SB, Tae WS, Seo DW, Kim SE. Partial seizures manifesting as apnea only in an adult. *Epilepsia* 1999; **40:** 1828–31.

49 So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. *Epilepsia* 2000; **41:** 1494–97.

50 McLean BN, Wimalaratna S. Sudden death in epilepsy recorded in ambulatory EEG. *J Neurol Neurosurg Psychiatry* 2007; **78:** 1395–97.

51 Thomas P, Landré E, Suisse G, Breloin J, Dolisi C, Chatel M. Syncope anoxo-ischémique par dyspnée obstructive au cours d'une crise partielle complexe temporale droite. *Epilepsies* 1996; **8:** 339–46.

52 Espinosa PS, Lee JW, Tedrow UB, Bromfield EB, Dworetzky BA. Sudden unexpected near death in epilepsy: malignant arrhythmia from a partial seizure. *Neurology* 2009; **72:** 1702–05.

53 Bateman LM, Spitz M, Seyal M. Ictal hypoventilation contributes to cardiac arrhythmia and SUDEP: report on two deaths in video-EEG-monitored patients. *Epilepsia* 2010; **51:** 916–20.

54 Gastaut H, Fisher-Williams M. Electro-encephalographic study of syncope; its differentiation from epilepsy. *Lancet* 1957; **273:** 1018–25.

55 Ryvlin P, Tomson T. Mortemus (Mortality in epilepsy monitoring unit study): preliminary findings. *Epilepsia* 2009; **50** (suppl 4)**:** 60.

56 Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy: clinical and neurophysiologic features. *Epilepsia* 2003; **44:** 179–85.

57 Schuele SU, Bermeo AC, Alexopoulos AV, et al.Video-electrographic and clinical features in patients with ictal asystole. *Neurology* 2007; **69:** 434–41.

58 Rossetti AO, Dworetzky BA, Madsen JR, Golub O, Beckman JA, Bromfield EB. Ictal asystole with convulsive syncope mimicking secondary generalisation: a depth electrode study. *J Neurol Neurosurg Psychiatry* 2005; **76:** 885–87.

59 Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992; **42:** 1727–32.

60 Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004; **364:** 2212–19.

61 Schott GD, McLeod AA, Jewitt DE. Cardiac arrhythmias that masquerade as epilepsy. *Br Med J* 1977; **1:** 1454–57.

62 Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. *Epilepsy Res* 1998; **30:** 77–83.

63 Ronkainen E, Ansakorpi H, Huikuri HV, Myllylä VV, Isojärvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2005; **76:** 1382–86.

64 Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart-rate variability in localization-related epilepsy. *Epilepsia* 2007; **48:** 917–22.

65 Adjei P. Autonomic dysfunction in epilepsy. PhD thesis, University College London, 2010.

66 Terrence CF, Rao GR, Perper JA. Neurogenic pulmonary edema in unexpected, unexplained death of epileptic patients. *Ann Neurol* 1981; **9:** 458–64.

67 Natelson BH, Suarez RV, Terrence CF, Turizo R. Patients with epilepsy who die suddenly have cardiac disease. *Arch Neurol* 1998; **55:** 857–60.

68 Opeskin K, Thomas A, Berkovic SF. Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy? *Epilepsy Res* 2000; **40:** 17–24.

69 Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005; **65:** 1021–5.

70 Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? *Epilepsy Res* 2009; **87:** 277–80.

71 Oppenheimer S. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. *Clin Auton Res* 2006; **16:** 6–11.

72 Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest* 1996; **109:** 1215–21.

73 Roche F, Reynaud C, Pichot V, et al. Effect of acute hypoxia on QT rate dependence and corrected QT interval in healthy subjects. *Am J Cardiol* 2003; **91:** 916–19.

74 Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. *Neurology* 1984; **34:** 255–57.

75 Goldman AM, Glasscock E, Yoo J, Klassen TL, Noebles JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. *Sci Transl Med* 2009; **1:** 98–106.

76 Hindocha N, Nashef L, Elmslie F, et al. Two cases of sudden unexpected death in epilepsy in a GEFS+ family with an *SCN1A* mutation. *Epilepsia* 2008; **49:** 360–65.

77 Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. *Brain Pathol* 2011; **21:** 201–08.

78 Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. *J Neurosci* 2010 **30:** 5167–75.

79 Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. *Ann Neurol* 2010; **68:** 787–96.

80 Nashef L, Garner S, Sander JWAS, Fish DR, Shorvon SD. Circumstances of death in sudden death in epilepsy: Interviews of Bereaved Relatives. *J Neurol Neurosurg Psychiatry* 1998; **64:** 349–52.

81 Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 2000; **68:** 211–13.

82 Shoja MM, Tubbs RS, Malekian A, Jafari Rouhi AH, Barzgar M, Oakes WJ. Video game epilepsy in the twentieth century: a review. *Childs Nerv Syst* 2007; **23:** 265–67.

83 Téllez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Res* 2005; **65:** 101–15.

84 Monté CPJA, Arends JBAM, Tan IY, Aldenkamp AP, Limburg M, de Krom MCTFM. Sudden unexpected death in epilepsy patients: risk factors, a systematic review. *Seizure* 2007; **16:** 1–7.

85 Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav* 2002; **3:** 338–42.

86 Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. *Neurology* 2008; **71:** 1572–78.

87 Williams J, Lawthom C, Dunstan F, et al. Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis at autopsy. *J Neurol Neurosurg Psychiatry* 2006; **77:** 481–84.

88 Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res* 2003; **57:** 69–75.

89 Surges R, Taggart P, Sander JW, Walker MC. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. *Epilepsia* 2010; **51:** 738–44.

90 Nilsson L, Bergman U, Diwan W, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. *Epilepsia* 2001; **42:** 667–73.

91 Aurlien D, Tauboll E, Gjerstad L. Lamotrigine in idiopathic epilepsy—increased risk of cardiac death? *Acta Neurol Scand* 2007; **115:** 199–203.

92 Beran RG, Weber S, Sungaran R, Venn N, Hung A. Review of the legal obligations of the doctor to discuss Sudden Unexplained Death in Epilepsy (SUDEP)—a cohort controlled comparative cross-matched study in an outpatient epilepsy clinic. *Seizure* 2004; **13:** 523–28.

93 Ryvlin P, Rheims S. Increased risk of SUDEP among epileptic patients receiving placebo in randomised controlled trials. *Epilepsia* 2009; **50** (suppl 11)**:** 223.

94 Hancox JC, Witchel HJ. Psychotropic drugs, hERG, and the heart. *Lancet* 2000; **356:** 428.

95 Arshad A, Mandava A, Kamath G, Musat D. Sudden cardiac death and the role of medical therapy. *Prog Cardiovasc Dis* 2008; **50:** 420–38.

96 Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. *Epilepsia* 2006; **47:** 21–26.

97 Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. *Epilepsia* 2010; **51:** 2211–14.

98 Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. *Ann Neurol* 1999; **46:** 45–50.

99 Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* 2002; **43:** 170–74.

100 Bell GS, Sinha S, Tisi J, et al. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? *J Neurol Neurosurg Psychiatry* 2010; **81:** 716–18.

101 Sperling MR, Harris A, Nei M, Liporace JD, O'Connor JO. Mortality after epilepsy surgery. *Epilepsia* 2005; **46** (suppl 11)**:** 49–53.

102 Salanova V, Markand O, Worth R. Temporal lobe epilepsy: analysis of failures and the role of reoperation. *Acta Neurol Scand* 2005; **111:** 126–33.

103 Jehi L. Sudden death in epilepsy, surgery, and seizure outcomes: the interface between heart and brain. *Cleve Clin J Med* 2010; **77** (suppl 3)**:** S51–55.

104 Åmark P, Stödberg T, Wallstedt L. Late onset bradyarrhythmia during vagus nerve stimulation. *Epilepsia* 2007; **48:** 1023–24.

105 Tatum WO 4th, Moore DB, Stecker MM, et al. Ventricular asystole during vagus nerve stimulation for epilepsy. *Neurology* 1999; **52:** 1267–69.

106 Ardesch JJ, Buschman HP, van der Burgh PH, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. *Clin Neurol Neurosurg* 2007; **109:** 849–52.

107 Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology* 2000; **55:** 1002–07.

108 Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. *Neurology* 2000; **55:** 1450–54.

109 So NK, Sperling MR. Ictal asystole and SUDEP. *Neurology* 2007; **69:** 423–24.

110 Schuele SU, Bermeo AC, Locatelli E, Burgess RC, Luders HO. Icatl asystole: a benign condition? *Epilepsia* 2008; **49:** 168–71.

111 Lim ECH, Lim S-H, Wilder-Smith E. Brain seizes, heart ceases: a case of ictal asystole. *J Neurol Neurosurg Psychiatry* 2000; **69:** 557–59.

112 Lather CM, Schraeder PL. Stress and sudden death. *Epilepsy Behav* 2006; **9:** 236–42.

113 Yuen AW, Thopson PJ, Flugel D, Bell GS, Sander JW. Mortality and morbidity rates are increased in people with epilepsy: is stress part of the equation? *Epilepsy Behav* 2007; **10:** 1–7.

114 Beran RG. SUDEP—to discuss or not discuss: that is the question. *Lancet Neurol* 2006; **5:** 464–65.

115 Brodie MJ, Holmes GL. Should all patients be told about sudden unexpected death in epilepsy (SUDEP)? Pros and cons. *Epilepsia* 2008; **49** (suppl 9)**:** 99–101.

116 Morton B, Richardson A, Duncan S. Sudden unexpected death in epilepsy (SUDEP): don't ask, don't tell? *J Neurol Neurosurg Psychiatry* 2006; **77:** 199–202.

117 National Highway Traffic Safety Administration, Fatality analysis reporting system (FARS) encyclopedia. http://www-fars.nhtsa.dot.gov/Main/index.aspx (accessed March 10, 2011).

118 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;**345:** 631–37.

119 Schraeder PL, Delin K, McClelland RL, So EL. Coroner and medical examiner documentation of sudden unexplained deaths in epilepsy. *Epilepsy Res* 2006; **68:** 137–43.

120 Thom M. The autopsy in sudden unexpected death in epilepsy. *Curr Diagn Pathol* 2007; **13:** 389–400.