



Sudden unexpected death in epilepsy

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Mortality in people with epilepsy is two- to three-times that of the general population. This can be attributed to epilepsy itself (epilepsy-related death) or to the underlying cause of the epilepsy. Sudden unexpected death in epilepsy (SUDEP) is the commonest cause of epilepsy-related death. It is a syndrome where a person with epilepsy dies suddenly and no other cause of death is found. There are frequent reports of persons dying alone in their sleep. It is assumed that death occurs following a seizure but since the deaths are often unwitnessed this is only an assumption. The most important risk factor appears to be poor seizure control. Lately, SUDEP has received much public interest, has been the subject of international forums, ethical debates and comprises part of national guidelines on epilepsy management. Despite its high profile, the evidence for specific risk factors and pathophysiology is still not established. Poor incident case reporting, inaccurate death certification and fewer post-mortem examinations have limited the value of epidemiological data on SUDEP. Here, we review the characteristics of SUDEP, its likely risk factors, mechanisms and differential diagnosis, and consider possible strategies for prevention. We also explore the discussion of SUDEP with patients and the management of relatives of SUDEP patients.

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Historical perspective

Deaths resulting from epilepsy and sudden unexpected death in epilepsy (SUDEP) in particular are not new concepts. In the late 19th century, the *Lancet* reported epilepsy-related death in four groups: from the epilepsy itself, from 'sudden deaths in a fit', from 'deaths after a rapid succession of fits' and 'deaths from accidents' [1]. However, until recently there has been a distinct scarcity of information on SUDEP in the medical literature and public information.

George Washington's daughter

George Washington's personal diary describes the epilepsy of his stepdaughter, Patsy Custis, who had 'seized with fits' from an early age in stereotyped attacks, which had been uncontrolled by the treatments of the time [2]. In 1773, he described her sudden death during or shortly after a seizure.

Prince John

The story of Prince John, the youngest child of George V, who died from epilepsy in 1919

when aged 13 years, epitomized the secrecy and stigma surrounding death from epilepsy. His death had been hidden from the public until 1998 when photographs of the Prince, owned by the Duke and Duchess of Windsor, were published for the first time, and are now available on the Epilepsy Bereaved website [101]. He had epilepsy and autistic learning difficulties and was sheltered from public view, prevented from participating in public life and increasingly isolated from his family [102,103]. The Royal Doctor, Alan Reeve Manby, had recorded:

"His Royal Highness Prince John, who has since infancy suffered from epileptic fits, which have lately become more frequent and severe, passed away in his sleep following an attack this afternoon at Sandringham" [103].

Even today there is a social taboo of epilepsy [101]; individuals with epilepsy are still often disadvantaged physically, psychologically and financially. This in part explains why individuals, the medical profession and political leaders still fail to afford epilepsy and SUDEP the attention it clearly deserves [101].

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Mortality in epilepsy

Epilepsy is associated with a two- to threefold increase in mortality compared with an age-matched population [3]. Meta-analyses have demonstrated overall standardized mortality ratios (SMRs) of 1.2–9.3, with variations owing largely to differences in source population [4]. The prospective UK National General Practitioner Study of newly diagnosed epilepsy gave an SMR of 3.0 (95% confidence interval [CI]: 2.5–3.7) [5]. The causes of death in epilepsy vary according to the study population. The commonest causes of community deaths are pneumonia, cerebrovascular disease and CNS and non-CNS-related neoplasia, whereas SUDEP is much more common in hospital populations [3]. Epilepsy, and subsequently SUDEP, are important considerations in mortality in pregnancy, justifying special management arrangements for pregnant women with epilepsy (see later).

The increased mortality among patients with epilepsy is attributable both to the underlying disease and to the epilepsy itself (BOX 1) [6]. The underlying cause of epilepsy clearly contributes to the overall mortality. Symptomatic epilepsies, therefore, carry a higher mortality than idiopathic epilepsies, owing to underlying causes, such as primary and secondary brain tumors and cerebrovascular disease. SUDEP is the commonest cause of epilepsy-related death (see later) [6–8].

Status epilepticus (including nonconvulsive status) carries considerable mortality, with rates between 0.5 and 10% of all deaths in epilepsy [4]. It has a bimodal age of incidence, peaking in the first year of life and again after 60 years of age [4]. It is frequently associated with the sequelae of cardiac arrests and myocardial infarction [4].

Box 1. Causes of death in epilepsy.

- *Direct*
 - SUDEP
 - Status epilepticus
- *Indirect*
 - Accidents caused by seizures
 - Aspiration pneumonia after seizures
 - Iatrogenic
 - Drug toxicity
 - Suicide
- *Underlying disease-related deaths*
 - Primary and secondary CNS neoplasia
 - Cerebrovascular disease
 - CNS infections
 - Neurodegenerative disorders
- *Deaths unrelated to epilepsy*
 - Non-CNS neoplasia
 - Ischemic heart disease
 - Pneumonia
 - Accidents unrelated to seizures

SUDEP: Sudden unexplained death in epilepsy.
Adapted from [3].

Accidental deaths in people with epilepsy result from drowning, road traffic accidents, falls and burns [4], and account for 1–16% of deaths in people with epilepsy [9]. People with epilepsy are at increased risk of fatal accidents compared with the background population. The large majority of accidental deaths caused by epilepsy occur while swimming or bathing: a Canadian study identified that 5% of all drownings were attributable to seizures, 60% occurred in bathtubs [10].

Suicide

Psychiatric symptoms are very common in epilepsy, especially depression [11]. Suicide risk is increased threefold in epilepsy [12] and appears highest in those with temporal lobe epilepsy [13], and in those with refractory epilepsy and/or psychiatric comorbidity [14]. Patients with newly diagnosed epilepsy appear to be a particularly vulnerable group [12].

SUDEP

Definition

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a structural or toxicological cause for death [15].

In 1997, an expert panel suggested that if all following criteria were met, then SUDEP could be considered 'definite' [16]:

- A diagnosis of epilepsy
- Death occurring unexpectedly while in a reasonable state of health
- Death occurring suddenly
- Death occurring in normal activities and benign circumstances
- Not finding an obvious medical cause of death during post-mortem examination
- Death not resulting from trauma, asphyxia due to aspiration or intractable status epilepticus

Without post-mortem evidence, SUDEP can only be considered as 'probable'. Establishing a definite diagnosis of SUDEP remains difficult. Lack of consistency in death certification, insufficient information regarding the circumstances of such deaths and the declining numbers of post-mortem examinations have hindered the interpretation of SUDEP statistics [17].

Incidence

Annual incidence

The annual incidence of SUDEP varies according to the severity of the epilepsy and frequency of seizures. Thus, overall incidence studies have demonstrated highest rates among patients who are considered epilepsy surgical candidates (although rates are low after successful epilepsy surgery [18]), those undergoing vagus nerve stimulation, those who have attended epilepsy referral centers or those involved in antiepileptic drug (AED) trials [6]. Among prevalent community cases, the incidence is less than one per 1000 person-years [19], whereas among cohorts awaiting epilepsy

surgery it is one per 100 person-years [8]. In a population-based study of incident cases of epilepsy, the SUDEP incidence was 0.35 per 1000 patient-years, 24-fold higher than that expected in the general population [7]. SUDEP incidence was intermediate in those with intellectual disability (3.4–3.6 per 1000 patient-years) and in children (0–0.2 per 1000 patient-years) [6].

Age-specific incidence

The commonly held view that SUDEP is rare in very young and elderly populations has not been vigorously tested, since most studies of epilepsy-related death have included only patients within pre-defined age ranges.

Children

SUDEP is often reported as relatively rare in children [20], despite children with epilepsy having a more than fivefold risk of dying in the first 15–20 years after diagnosis. However, most of these excess deaths relate to comorbid neurological disorders and dysfunction, rather than to SUDEP [21,22].

Elderly

SUDEP is less commonly considered in the elderly, but is unlikely to be as rare as usually reported [23]. Sudden deaths in elderly patients with epilepsy are easily attributed to comorbidities, for example cardiovascular or pulmonary disease, or even to old age itself, rather than to SUDEP.

Risk factors

Several authors have attempted to identify potential risk factors and clinical characteristics that might place epilepsy patients at risk of SUDEP. These have largely been inferred from retrospective studies, often lacking appropriate controls, or are derived from highly selected groups, such as patients attending epilepsy centers. Suspected risk factors for SUDEP include:

- Young adults: SUDEP occurs at all ages although the risk appears highest aged 20–40 years;
- Long epilepsy duration: most studies report a mean epilepsy duration in SUDEP cases of 15–20 years [7], implying earlier epilepsy onset in most cases;
- Generalized tonic-clonic seizures (GTCS) have occurred in up to 90% of SUDEP cases [7] and often with reports of GTCS several hours before or immediately before death [6];
- Frequent seizures appear a strong risk factor for SUDEP, with a 23-times relative risk in those with one seizure per observed year compared with those who had been seizure free [23]. In the same study, the relative risk for SUDEP was 10.16 in patients with more than 50 seizures per year compared with patients who had two or fewer seizures per year. SUDEP is rare in patients who have been seizure-free for over 1 year; only a few such cases have been reported [7,24];
- AED polytherapy: patients taking multiple AEDs, especially three or more, are at increased SUDEP risk compared with those receiving monotherapy [7,24,25]. This most likely reflects more severe epilepsy requiring more AEDs to achieve seizure

control. It seems counterintuitive to suggest a role for AEDs themselves as a risk factor, given their aim of trying to reduce seizure frequency;

- Variable AED ingestion and non-compliance: abrupt AED withdrawal [26] and frequent AED dose changes [27] appear potential risk factors for SUDEP. It is notoriously difficult to assess AED compliance after death. Nevertheless, it is reasonable to suppose that taking AEDs regularly will reduce the likelihood of seizures and should help to reduce the risk of SUDEP (see compliance section);
- Being alone: only 10% of SUDEP cases are witnessed, most of which are associated with a GTCS [7]. Of patients dying during unwitnessed events, 30–50% are found dead in bed [24], with 71% of cases found in the prone position [28,29];
- Other factors: various studies have implicated other possible risk factors for SUDEP including: male sex, ethnicity, severe intellectual disability, recent head injury, structural brain lesions, being at home, stressful life events, psychotropic and anxiolytic drugs, and alcohol abuse [3,7].

Designing studies to identify SUDEP risk factors is difficult and requires a population-based case-control study with incidence density sampling, where cases and controls are ascertained from the same source population of people with epilepsy.

Pathophysiology

SUDEP is a heterogeneous syndrome, probably with several different causes. A seizure seems invariably the trigger, but death during that seizure also implies an idiosyncratic cardiorespiratory vulnerability.

Seizure related

SUDEP is widely accepted as a seizure-related event [4,8,24]. However, since most cases are unwitnessed, it may be impossible to know if a seizure had definitely occurred, let alone whether the death occurred during (peri-ictally) or after a seizure (post-ictally). Sometimes there is circumstantial clinical evidence of a recent seizure with a fresh tongue bite or disrupted bedclothes, but the absence of these clearly does not exclude a seizure.

Cardiorespiratory vulnerability

Cardiac and respiratory mechanisms are difficult to separate and probably contribute together in causing SUDEP. A total of 50–86% of SUDEP post-mortem cases show pulmonary edema, cardiac enlargement and hepatic congestion (indicative of right-sided heart failure), each insufficient themselves to cause death [16,29,30]. However, these findings do not distinguish apnea from cardiac arrest as the cause. Some reported cases seem to have both respiratory and cardiac causes. For example, a 20-year-old female with a previous cardiorespiratory arrest during status epilepticus [31] had a short convulsive seizure during video telemetry. Post-ictally she developed persistent apnea, without ventilatory effort. The initial cardiac rhythm was normal for 10 s, but then slowed to cardiac arrest. Examination after resuscitation showed no airway obstruction or pulmonary edema.

Ventilatory factors

Proposed respiratory mechanisms of SUDEP relate to possible central or obstructive apnea [32], excess bronchial and oral secretions, and pulmonary edema, all of which may occur in SUDEP cases [24,33,34]. Ventilatory changes, and particularly central hypoventilation, commonly accompany seizures, probably through epileptic activity spreading to cerebral respiratory centers [32] followed by a secondary endogenous opioid release [19]. Secondary seizure-related hypercapnia and hypoxia appear less potent influences on respiratory neurons.

The fact that most SUDEP occurs when alone suggests that lack of external stimulation during or following a seizure may be important. The spectrum of ventilatory responsiveness to CO₂ during a rebreathing protocol in the general population is very broad [34]. It is plausible that some individuals who tolerate high CO₂ partial pressure (Pa) levels sometimes need external stimulation to restart breathing after a seizure.

Animal work supports central respiratory depression as a mechanism for SUDEP in a sheep model in which epileptic seizures were chemically induced [35]. Those sheep that died showed a simultaneous fall in PaO₂ and rise in pulmonary artery and left atrial pressures, causing pulmonary edema, and had higher pulmonary vascular pressures and showed hypoventilation. Thus, the development of pulmonary edema, a frequent finding at SUDEP post mortem and occasionally observed after a seizure, is consistent with hypoventilation alone rather than necessarily requiring cardiac arrest.

One reported case developed SUDEP several months following an episode of seizure-related pulmonary edema [36]. Pulmonary edema accompanying a seizure is therefore extremely important and potentially a marker of 'near-death' experience, prompting risk-factor modification or initiation of appropriate prophylactic measures.

Some SUDEPs appear associated with intrinsic or extrinsic mechanical obstruction, for example cases found lying in a prone position with resultant nose and mouth obstruction against the bed clothing [32]. The prone position might also impede ventilation by decreasing vital capacity and tidal volume, especially after exercise [37]. Seizure-related obstructive apnea might also result from the combination of hypotonia of the respiratory muscles and bronchial spasms during seizures [31]. Asphyxia may not be specifically excluded through post mortem. Petechial hemorrhages are not specific and occur in hypoxia and as a result of raised cephalic pressure, both of which can be found during a seizure or resuscitation. It is not known whether smoking status or respiratory comorbidities, such as asthma, chronic obstructive pulmonary disease or emphysema, in individuals contribute to the risk of SUDEP [32].

Cardiac factors

Some SUDEP cases appear to result primarily from cardiac causes, perhaps through cardiac arrhythmia, myocardial ischemia, electrolyte disturbance, autonomic imbalance, hypoxia and potentially arrhythmogenic drugs.

Arrhythmias are commonly suggested as the causal mechanism in SUDEP [37]. The exact pathophysiological mechanisms remain unclear, but theories surround cardiorespiratory dysregulation which predisposes to fatal cardiac arrhythmias, central hypoventilation or apnea. Experimental work by Lather and Schraeder demonstrated, using animal cat models, that autonomic dysfunction was associated with both interictal and ictal epileptogenic activity. This was demonstrated by administering intravenous pentylentetrazol to anaesthetized cats which showed that autonomic cardiac nerves did not respond in a predictable manner to changes in blood pressure, with a marked increase in variability in mean autonomic cardiac discharge and the appearance of very large increases, firstly in the variability of the discharge of the parasympathetic nerves, and then secondly in sympathetic discharge. It was shown that the altered autonomic cardiac nerve discharge was associated with interictal epileptogenic activity and arrhythmia, and was proposed that it potentially contributes to mechanisms in the pathophysiology of SUDEP [38–40].

Cardiac arrhythmias are common in seizures, especially GTCS and temporal lobe seizures [41,42]. Malignant tachy- or bradyarrhythmias, or sinus arrest can occur secondary to the ictal discharge or apnea period [19,32,33]. Indeed, one study demonstrated that 21% of drug-resistant epilepsy patients had an episode of ictal bradycardia or asystole that required permanent cardiac pacing [43].

The most serious arrhythmia of asystole is of interest, and may prove to be a point of differentiation from SUDEP in young people with normal hearts and no cardiac conduction defects. The limited human literature tends to suggest a direct CNS effect on heart rhythm. Experiments utilized direct stimulation of sites in temporal limbic structures, the frontal lobe and the insula with implantable electrodes, which resulted in changes in heart rate and blood pressure to the point of asystole [44]. They demonstrated that ictal asystole is more common in temporal lobe epilepsy than in extratemporal lobe epilepsy; results in generalized epilepsy were not reported [45]. However, sinus pauses and brief sinus arrest also occur not infrequently in different types of syncope, and generally are thought of as benign in individuals with normal cardiac structure and function. Therefore, clinicians should be alert to the occurrence of ictal arrhythmias, should have a low threshold for cardiac monitoring and investigations and should aim for an improved seizure control, as this currently seems to be the best measure in averting SUDEP and or fatal arrhythmias [44].

Although most cardiac-related SUDEP appear to be due directly to arrhythmias resulting from ictal discharge (primary) [19,34], there may also be long-term changes in the neuronal network of cardiac tissues due to the cardiovascular effects of repeated major seizures (secondary) [19]. Pre-existing incidental cardiac disease, especially in the elderly, may also increase vulnerability to fatal arrhythmias during seizures. There is also the possibility of a channelopathy, leading simultaneously to both seizures and arrhythmias [19].

The role of arrhythmogenic side effects of any AED in SUDEP remains inconclusive. QT interval prolongation, resulting from the seizure or as an inherited cardiac trait, may contribute [34]. For example, the QTc interval appeared to be prolonged in patients who subsequently died from SUDEP when examined on single-lead ECG tracings obtained during EEG recordings [46].

Post-mortem examination in SUDEP patients will not, by definition, reveal a cause of death. However, SUDEP cases have more dilated and heavier hearts than expected [16]. Pulmonary edema is common. Sometimes there are also heart muscle pathological changes, including coronary artery and interstitial fibrosis, leukocytic infiltration, edema and morphological abnormalities of the conduction system [29,32]. The relevance of these findings from small studies remains unclear.

Differential diagnosis

It is important to always consider other potential causes of sudden death in a suspected case of SUDEP. Primary cardiac arrhythmias are the most important differential diagnosis. These include long QT syndromes, for example, Romano–Ward syndrome (autosomal dominant), Jervell–Lange Nielsen syndrome [19] (autosomal recessive), Brugada syndrome and Wolf–Parkinson–White syndrome. Others have structural heart disease, for example, hypertrophic cardiomyopathy and aortic stenosis. Therefore, the importance of such an alternative diagnosis for family members goes beyond the tragic death of a loved one, since there may be important genetic implications; genetic counseling, screening or the opportunity of potentially preventative and therapeutic options for at risk individuals are important. Less common differential diagnoses of SUDEP cases include toxic or metabolic causes such as hypoglycemia.

Prevention

With no clear mechanism for SUDEP, any suggested preventative measures remain speculative. However, minimizing the risk of SUDEP involves optimizing the clinical management of epilepsy, and so has a wider benefit to the epilepsy population.

Optimizing epilepsy management

Diagnostic certainty

The diagnosis of epilepsy is clinical and relies on accurate personal and eye-witnessed accounts, concentrating on the circumstances of the episode, the preceding aura, the interictal state and postictal events. The diagnostic possibilities of an episode of altered consciousness are vast. All relevant information must be obtained before a diagnosis of epilepsy is made, including the identification of potential triggers and provoking factors. The clinical history must include a full past medical history, including any previous significant head injury, meningitis or encephalitis, a birth history, any history of febrile convulsions and any family history of epilepsy.

Investigations

All individuals in whom epilepsy is suspected must be investigated appropriately. Investigations include EEG and brain imaging (usually MRI), which may support the diagnosis but are

themselves not sufficient to make a diagnosis. A 12-lead ECG, although rarely abnormal [47], should form part of the diagnostic work-up of all patients under investigation for an episode of unexplained loss of consciousness and, therefore, also in those in whom epilepsy is suspected.

Giving the diagnosis

A diagnosis of epilepsy is a life-changing event with potential psychological consequences; the diagnosis should be given and relevant treatment begun only when there is reasonable certainty. On first contact with the patient all the relevant information may not be at hand; the passage of time can be an important diagnostic tool in avoiding misdiagnosis.

Additional investigations

Specific cardiac investigation

There is a risk that some cases labeled as SUDEP were actually inherited arrhythmias misdiagnosed as epilepsy. It has even been suggested that a cardiologist should evaluate all patients with presumed epilepsy [32]. The cardiological examination would comprise the personal and family clinical history, a physical examination of the cardiorespiratory system and a 12-lead resting ECG, as well as, if indicated, echocardiography and an ambulatory 24-h ECG monitoring [32]. If these investigations were inconclusive and a cardiac cause still possible, tilt-table studies and prolonged ambulatory loop ECG recording could also be performed. This detailed cardiac investigation of patients with a clinical diagnosis of epilepsy has not been studied systematically. However, combined ambulatory ECG/EEG monitoring in patients with epilepsy identified high-risk arrhythmias in only 5% of 338 patients, a rate similar to healthy asymptomatic adults [48]. It has also been suggested that family members of SUDEP victims should undergo cardiac investigations to search for inherited potentially lethal cardiac diseases [49]. There is no good evidence to suggest the need for additional cardiac investigations in patients with epilepsy unless there are specific indications.

Improving seizure control

Given that SUDEP appears to be a seizure-related event, with increased incidence in refractory cohorts, improving seizure control is probably therefore the most important measure to prevent SUDEP [32]. An important part of this is to improve medication compliance (see later).

Antiepileptic medication

When to treat?

The risk of SUDEP has occasionally been considered grounds for prescribing AEDs after a single seizure. However, the risk of SUDEP in the Multi-Centre Epilepsy and Single Seizures (MESS) study [50] was no different among the group randomized to immediate AED compared with those randomized to delayed treatment. Thus, although it is true that rarely patients die from SUDEP having had only one previous GTCS, there is no evidence that treating with AEDs after a single seizure prevents SUDEP overall.

Specific AEDs

No one AED appears safer than any other in terms of an association with SUDEP. Carbamazepine was initially suggested as a risk factor, after its increased use had been identified among SUDEP cases attending an epilepsy clinic [51]. Other studies have not replicated this association although one group did observe a small (not statistically significant) increased SUDEP risk with carbamazepine and oxcarbazepine treatment [29]. The pragmatic multicenter Standard and New Antiepileptic Drugs (SANAD) study demonstrated in large patient numbers that no one drug (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate or valproate) was associated with an increased risk of death than any other drug [52]. There is also no conclusive evidence that carbamazepine either slows atrioventricular conduction [53] or prolongs the QT interval and no evidence to avoid any particular AED through its SUDEP risk [54].

Compliance

A history of AED compliance obtained from a third party is notoriously unreliable. Previous studies of compliance following epilepsy-related death have given conflicting results. One retrospective study suggested the greatest risk was in those with unstable, irregular and less well-controlled epilepsy, and that poor or erratic compliance may be a causative factor [55]. Patients who had undergone regular therapeutic drug monitoring by blood testing had half the risk of SUDEP compared with patients who were not monitored [56]. However, in this study the observed variability of blood AED levels, reflecting medication compliance, was similar in the two groups, and so there was no definite evidence of noncompliance amongst SUDEP cases.

Post-mortem AED levels are unreliable owing to tissue redistribution of drugs following death [57], and hence subtherapeutic post-mortem blood levels do not necessarily reflect previous poor compliance. Furthermore, certain drugs, such as phenytoin, can undergo changes at post-mortem [5]. Opeskin *et al.* compared post-mortem blood AED levels from patients following SUDEP and non-SUDEP deaths, and found no difference in the likelihood of blood AED concentrations being undetectable, subtherapeutic or therapeutic between these groups [58]. They therefore came to the surprising conclusion that AED compliance was not an important factor leading to SUDEP.

In a recent study, post-mortem hair AED concentrations demonstrated that observed variability in AED-taking behavior was significantly greater in patients who had died from SUDEP compared with epilepsy outpatients or inpatients [59]. The most likely explanation was greater variability in AED ingestion among SUDEP patients. Therefore, the authors concluded that SUDEP, at least in a proportion of cases, is preventable and that emphasizing adherence to AED medication appears essential.

Pregnancy

SUDEP has been reported to be commoner in young males [24]; however, the possibility of worsened seizure control during pregnancy potentially putting women at particular risk of

SUDEP is also an important consideration [104]. During pregnancy, the plasma levels of AEDs may decline; this is mainly attributed to vomiting, changes in volume of distribution and changes in protein binding. However, a major factor is likely to be the deliberate reduction or cessation of drug taking by women with epilepsy who are planning to, or having become pregnant [60] because of concern about adverse effects of drugs on the fetus. Thus, there is a conflict in the care of epilepsy in pregnancy. A reduction or cessation of therapy is probably better for the fetus. However, this does increase the risk of seizures, and poorly controlled epilepsy increases the risk of SUDEP.

The possibility of SUDEP should be mentioned to all women who plan to stop anticonvulsant therapy in order to become pregnant. Fortunately, it is very rare in those with well-controlled epilepsy. Women with epilepsy need specific specialist advice in pregnancy, ideally in a dedicated clinic to encompass pre-pregnancy counseling and attended by an obstetrician, neurologist/obstetric physician and a specialist midwife or neurological nurse.

Epilepsy surgery

Patients considered suitable for epilepsy surgery have a high risk of SUDEP owing to their poor seizure control [8]; successful epilepsy surgery dramatically reduces this risk [18]. When discussing risks of epilepsy surgery with patients, it is worth remembering that the mortality of surgery for epilepsy (approximately 1%) is actually comparable to the 1-year risk of not having an operation (1% per year in candidates for epilepsy surgery).

Supervision

The benefits of improved supervision were clearly demonstrated in sudden infant death syndrome (SIDS). Here, the exact pathogenesis is also unknown and difficult to study. The Back to Sleep campaign from 1992 was associated with a 50% fall in SIDS incidence. The campaign encouraged parents and caregivers to sleep babies supine and to remove soft toys and soft bedding material from their environment to further reduce the risk of suffocation [61].

A similar case-control study in epilepsy suggested that nocturnal supervision could protect against SUDEP (odds ratio [OR]: 0.4; 95% CI: 0.2–0.8) when a supervising individual shared the same bedroom or when special precautions, such as a listening device, were employed (OR: 0.1; 95% CI: 0.0–0.3) [62].

Respiratory awareness

Hypoventilation as a likely cause of SUDEP suggests the need for intervention during seizures to ensure that breathing is adequate and remains adequate postictally. Other preventative measures might include the education of families, bed partners and carers who happen to witness seizures regarding repositioning of the patient to maintain and protect the airway, supervision until their breathing pattern normalizes and, if necessary, in stimulation of ventilation during seizures [32,33]. BOX 2 outlines suggested strategies in SUDEP prevention.

Box 2. Potential strategies for sudden unexplained death in epilepsy prevention.

- Supervision at nights – sharing rooms and seizure alarms
- Seizure supervision
- Carer education – breathing patterns, airway protection and stimulation
- Modify sleeping environment
- Optimize AED treatment
- Improve compliance and monitoring
- Minimize number of AEDs
- Stabilize AED regimen
- Consider surgery for refractory cases

AED: Antiepileptic drug.
Adapted from [61].

Specific preventative measures

Unfortunately there are as yet no specific measures or agents that have demonstrated effectiveness in preventing SUDEP. In rare patients who have experienced seizure-related pulmonary edema, a prophylactic α -blocker may be appropriate, although this remains to be proven [36]. They act by suppressing the effects of centrally generated sympathetic discharges and so may potentially be of use in averting SUDEP with the dual aim of preventing neurogenic pulmonary edema and CNS-generated cardiac arrhythmias. β -blockers have a well-established role in preventing cardiac arrhythmias, although are best avoided in the acute situation as they suppress myocardial contractility. The nonselective combined α - and β -adrenergic receptor blockers, such as labetalol or carvedilol, may prevent cardiac arrhythmias but provide less powerful α -blockade than the selective α -blockers and thus offer limited protection against neurogenic pulmonary edema. Therefore, with careful monitoring to prevent troublesome hypotension, the potential combination of a selective α -blocker and a β -blocker may offer optimal prophylaxis against both neurogenic pulmonary edema and malignant arrhythmias [36].

Discussing SUDEP

It would be naive to suppose that patients with epilepsy only learn of SUDEP from their clinician. Information and misinformation about SUDEP is widely available on the internet, and in magazines and newspapers; this availability of information is an important driver for epilepsy clinicians to discuss SUDEP with their patients.

There are no studies examining the impact of telling patients about SUDEP. Raising awareness of SUDEP should benefit more general epilepsy management; it should encourage better management of an acute seizure, better AED compliance, more rationalized drug therapy and avoidance of drug and alcohol abuse. However, others argue that warning patients

about a fatal outcome, where no proven pathophysiology, intervention or prevention exists, may adversely affect a patient's quality of life, by creating unnecessary anxiety and fear [63]. In 2006, only 5% of UK neurologists discussed SUDEP with all their patients, 26% with a majority, 61% with a few and 7.5% with none [64]. These results reflect individual patient autonomy, consent and the ethical principles of the patients' 'right to know', their 'right not to know' and the ethical principle of 'do no harm'. The commonest situation in which SUDEP was discussed was when asked or prompted to do so by the patient.

The ongoing ethical dilemma is not so much whether to discuss the issue, but what to say, how much to say and how best to say it. Patients differ in the quantity and type of information they want. A clinician's duty of care dictates a frank and open discussion with those who seek information. Several patient groups advocate a proactive and fully open approach and would wish to see information on SUDEP made much more accessible and included in patient information leaflets [24]. The evidence for patient benefit of such openness is currently lacking. The UK National Institute of Health and Clinical Excellence (NICE) advises that individuals with epilepsy and their families/carers should be given information on SUDEP [105]. However, clinical guidelines, although useful in standardizing care across regions, do not always reflect the complex interplay of an individual's medical and psychosocial situation. In the case of giving information on SUDEP, any guidelines are merely an overall guide or a prompt. A pragmatic approach, as reflected in the study of UK neurologists, is to approach this sensitive subject on an individual basis, driven by patients' individual risk factors and their need to discover information.

It is possible to give SUDEP information in a positive manner. By first acknowledging that SUDEP exists and that patients will hear about it from other sources, the clinician can set its likelihood in context for that individual, often reassuring the patient that although SUDEP is a remote possibility, for that individual it is very unlikely. This discussion may also help the patient to understand the importance of taking medication regularly, of appropriate safety precautions and of certain lifestyle adjustments such as control of alcohol consumption and regular sleeping hours. This discussion is best when supported by written information, such as a copy of the consultation letter. An example of such letter content (copied to the patient) might be as follows:

"We discussed her very low risk of SUDEP. I explained to her that the risk is increased in severe epilepsy and in those with seizures in sleep; it is less likely in those who take antiepileptic medication regularly and who avoid excess alcohol."

Managing bereaved relatives

The unexpected nature of SUDEP, its tendency to affect relatively young people and its unexplained mechanisms all undoubtedly compound the grief, sorrow, anger and denial among SUDEP relatives. An interview of bereaved relatives

outlined that most had been led to believe that epilepsy could not be fatal [24]. Limited research has demonstrated that relatives and friends of victims of SUDEP would have preferred to be told about its remote possibility [24].

The family doctor and the specialist should work together in providing early opportunities to meet relatives and to explain the unexplained nature of death, offer counseling from trained professionals, direct them towards self-help groups, and acknowledge and empathize with their sense of isolation, guilt and regret [24].

The future

Raising awareness

Raised awareness of SUDEP can be empowering for individual patients and helps patients to generate mature attitudes towards their epilepsy. Overall, epilepsy services are likely to improve with better knowledge of SUDEP among coroners, lay groups, relatives of SUDEP victims and politicians. Those involved in epilepsy management must continue to strive to transform the public image of epilepsy as a stigmatizing yet generally benign chronic illness, while also raising awareness of SUDEP as the most serious complication of epilepsy.

Post-mortem practice

Declining numbers of post-mortem examinations contribute to the deficient understanding of SUDEP. Although death and the circumstances surrounding SUDEP are clearly tragic and emotional, lay and medical communities must understand that a complete post-mortem examination is needed in a person with epilepsy who has died suddenly and unexpectedly.

Death certification

Correct certification of epilepsy deaths is essential. A SUDEP diagnosis should be recorded when post-mortem data sufficiently and convincingly support it. This should allow improved accuracy in data on SUDEP and other epilepsy-related deaths, and allows for the monitoring of trends in mortality. Unfortunately a US study showed that SUDEP was not cited consistently as the cause of death, even when diagnostic criteria were met [65].

Research

SUDEP is a heterogeneous condition with multifactorial causes and its exact mechanism remains unknown. There is a clear need for large, prospective, multicenter, case-control or cohort studies with regression analysis to help identify risk factors and hence indicate preventative strategies for patients with epilepsy [6].

The development of interventions and prevention of SUDEP first requires improved understanding of its cardiorespiratory mechanisms. Current interventions to prevent SUDEP are aimed at modifying suspected risk factors.

Research into SUDEP should focus on seizure prevention, the effect of therapy (mono- or polytherapy) on ictal, interictal and postictal states in relation to depressed consciousness, respiratory and cardiac variables [19], and postictal management.

The possible coexistence of both epilepsy and a liability to sudden cardiac death, for example in inherited sodium channelopathies, provides a useful research avenue. One approach to detecting occult arrhythmias would be for further long-term cardiac rhythm studies in people with epilepsy using implantable devices [19]. More importantly from the prevention viewpoint, however, is for coroners to begin systematic DNA collection and storage to allow identification of cardiac channelopathy genes in all cases of young sudden death.

Clinical practice could also be informed by research into optimizing the communication of risk effectively and of discussing SUDEP with patients, exploring the detrimental or positive influence of frank open discussion on patients' well-being and overall epilepsy management.

Expert commentary

A previous tendency to conceal epilepsy reinforced its social stigma and created a society where 'afflicted' individuals were hidden from public view. For many years there has been under-reporting of epilepsy and therefore of SUDEP. Even now the lack of acceptance of a uniform definition of SUDEP and the tendency for coroners and medical officers to avoid documenting SUDEP as the cause of death, even when the evidence is lacking for any other causes, has allowed inaccurate incidence data for SUDEP and epilepsy. This, in turn, has hindered research and slowed developments in the field.

Despite its high profile in clinical, political and lay arenas, and also in its recent incorporation into national epilepsy guidelines, the mechanisms of SUDEP, and hence its risk factors and preventative strategies, remain largely unknown.

Designing studies to ascertain potential risk factors for SUDEP is difficult. A proposed strategy would be a population-based case-control study with incidence density sampling, where cases and controls are ascertained from the same source population of people with epilepsy. Given the lack of knowledge surrounding its pathophysiology, professionals cannot advise on any proven preventative measures in SUDEP.

The decision on what to discuss with patients about SUDEP is generally determined on an individual basis, balancing a patient's desire to acquire knowledge regarding their condition against their autonomous right not to know. Each clinician's own knowledge about their patient's epilepsy, personality and psychosocial situation, their individual experience and that of others in the field will inform such discussions on SUDEP.

Five-year view

Raising awareness of SUDEP through the lobbying of lay patient and bereaved relative groups, and through the selective implementation of national epilepsy guidelines will provide an ideal platform on which to develop teams and networks for research in the field.

Increased awareness should prompt better reporting of SUDEP cases at post-mortem analysis and so improve national statistics of epilepsy and SUDEP. Detailed incident case

reporting together with further large, prospective, multicenter, case-control or cohort studies will help to identify or confirm proposed risk factors and disentangle its possible respiratory, cardiac and cerebral mechanisms.

The development and research into epilepsy genetics, and its interplay with inherited cardiac disorders are likely to provide clues in deciphering genetic predisposition towards SUDEP.

Networks of neurologists, epileptologists, nurse specialists, elderly and primary care physicians, and pathologists need to collaborate better with coroners, politicians, the pharmaceutical industry, researchers, scientists, and lay and bereaved relatives groups in determining the directions of research into epilepsy and SUDEP.

Conclusion

The recent public and medical debates, publications and the NICE guidelines on SUDEP are a timely reminder that epilepsy is far from a benign condition. SUDEP, the commonest cause of epilepsy-related death, is a heterogeneous condition for which the mechanisms remain uncertain, and for which specific risk factors for individuals remain largely undetermined.

The situation can only improve with better prospective incident case reporting by an improved accuracy in death certification and in pursuing post-mortem examinations. Meanwhile, clinicians should consider more open discussions with their patients, and particularly discussion on specific risks, aimed principally at improving epilepsy control. The complexity of epilepsy management and the unknowns of SUDEP require an effective working relationship between epilepsy specialists, epilepsy nurses and primary care teams to aid the unraveling of the complex associations of the medical and psychosocial factors involved in epilepsy, and ultimately in SUDEP.

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Key issues

- Sudden unexpected death in epilepsy (SUDEP) is the commonest cause of epilepsy-related death, with an annual incidence varying from less than one in 1000 to one in 100 person-years.
- SUDEP is a heterogeneous syndrome with no single defined mechanism; it may result when a seizure occurs in an individual with pre-existing (and as yet largely undetermined) cardiorespiratory vulnerability.
- Proposed mechanisms suggest a respiratory or cardiac cause, with theories surrounding prolonged apnea, cardiac arrhythmia, myocardial ischemia, electrolyte disturbance, autonomic imbalance, hypoxia, arrhythmogenic drugs, or central or obstructive apnea.
- Proposed risk factors include young age, male sex, ethnicity, poor antiepileptic drug (AED) compliance, multiple AED therapy, high seizure frequency, generalized tonic-clonic seizures, intellectual disability, recent head injury, structural brain lesions, sleeping prone, being at home and alcohol abuse.
- The most serious differential diagnosis of SUDEP is death from previously unrecognized inherited cardiac arrhythmias or from structural heart disease.
- A 12-lead ECG should be performed initially on all cases of first suspected seizure and unexplained epilepsy; where a cardiac cause for recurrent transient loss of consciousness is suspected, a cardiologist should see the patient and their ECG.
- Preventative strategies are speculative and incorporate seizure supervision and alarms, carer education, sleeping environment advice, rationalizing AED therapy and improving seizure control.
- The National Institute of Health and Clinical Excellence guidelines advise that 'individuals with epilepsy and their families/carers should be given and have access to information on SUDEP'; recent data suggest that only 5% of UK neurologists discuss SUDEP with all epilepsy patients.
- The decision to discuss or not to discuss SUDEP with patients should be on an individual basis and tailored to a patient's best interests.
- The future of research into the understanding SUDEP requires heightened awareness of the condition, improved accuracy in death certification and an increased practice of post-mortem examinations.
- Areas of research interest will concentrate on genetic causes of epilepsy, cardiac disorders, uniform pathophysiological mechanisms and understanding inherited tendencies for sudden death in epilepsy and/or cardiac disease.

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