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## Sudden unexpected death in epilepsy: a silent killer

(Index words: SUDEP, mortality, epilepsy, prevention, risk factors)

### Introduction

Epilepsy is a common neurological disorder with population prevalence rates ranging from 2.7 to 7.1 per 1000 people [1]. It has been estimated that 65 million people live with epilepsy worldwide [2]. Long-term, population based, prospective studies have shown an increased risk of premature mortality in patients with epilepsy by more than twice that of the general population [3-5]. The higher proportion of deaths in the epilepsy cohort is due to many aetiologies including malignant neoplasms, pneumonia and other respiratory diseases, cerebrovascular diseases and cardiovascular diseases [4, 5]. Causes of mortality as a direct consequence of seizures and epilepsy include sudden unexpected death in epilepsy (SUDEP), accidental deaths due to epileptic seizures and deaths from status epilepticus. SUDEP is the commonest cause of death directly attributable to epilepsy [6]. SUDEP is defined as 'sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a cause of death' [7].

### Epidemiology

The reported incidence rates are highly variable depending on the research methodology, the diagnostic criteria of SUDEP, and the study population. Patients with epilepsy have 24 times higher risk of sudden unexpected death compared with the general population [8]. A recent systematic review of pooled data from population-based epidemiological studies reported an annual incidence rate of 1.16 SUDEP cases per 1 000 patients with epilepsy and 0.81 cases per 100 000 population [9]. The risk is increased up to 5.9 per 1000 person-years in patients with chronic refractory epilepsy and 9.3 per 1000 person-years in patients who continue to have seizures after surgery for epilepsy [10]. SUDEP is rare among patients with epilepsy in remission. In the Medical Research Council Antiepileptic Drug Withdrawal Study, only two SUDEP cases were reported in over 5000 patient-years of those who had been in remission for two or more years [11]. SUDEP ranks second only to stroke, based on the years of potential life lost from neurological conditions [9]. Assuming the age of onset of epilepsy at 1, 15, and 30 years, the cumulative risk of SUDEP by age 70 has been estimated to be 8%, 7.2%, and 4.6% respectively [9]. These figures emphasise the public health impact of SUDEP.

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## Risk factors

A good understanding of risk factors is the foundation to formulate strategies for prevention of SUDEP. Many case-control studies have provided information on risk factors for SUDEP. Some studies have used living patients with epilepsy as controls, whereas others have used patients with epilepsy who have died of other causes. The Task Force on Epidemiology of the International League Against Epilepsy (ILAE) has published findings based on pooled data from major case-control studies [12]. Results from pooled data analysis indicate that males are at a slightly higher risk of SUDEP than females (odds ratio = 1.4) [12]. The highest risk for SUDEP is between ages 20 and 40 [13].

The risk is 1.95 times higher for those with duration of epilepsy for more than 15 years and 1.7 times higher for patients with onset of epilepsy before the age of 16 years [12]. The frequency of generalised tonic-clonic seizures (GTCS) is the most important risk factor for SUDEP. According to the pooled data analysis, the risk of SUDEP is 2.9 times higher for patients who experience one to two GTCS per year compared with those without GTCS. The risk gradually escalates with increasing GTCS frequency and the odds ratio is 14.5 for patients with more than 50 GTCS per year [12].

A case-control study found nocturnal seizures to be an independent risk factor for SUDEP [14]. Nocturnal seizures were associated with a 2.6 times higher risk of SUDEP after correction for previously established risk factors, and most sleep-related SUDEP occurred between 4 am and 8 am [14]. Epilepsy syndrome appears to be an important factor in the risk stratification. Idiopathic generalised epilepsy carries a lower risk [12], whereas Dravet syndrome is associated with a higher risk [15]. Post-ictal generalised EEG suppression (PGES) was found to be associated with SUDEP in a case-control study [16]. More recently, the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) investigated SUDEP cases in epilepsy monitoring units. In this study, all monitored SUDEP cases had PGES [17]. It is also possible that PGES is simply a marker of seizure-related hypoxia.

Some studies have described treatment with carbamazepine, lamotrigine and multiple antiepileptic drugs (AED) as risk factors for SUDEP [12]. This is a paradoxical finding as GTCS is a risk factor for SUDEP and treatment with AEDs is expected to reduce that risk. However, a recent study has revealed that AEDs, including carbamazepine and lamotrigine, either as monotherapy or polytherapy, do not increase the risk of SUDEP [18]. Furthermore, meta-analyses of randomised trials have identified that AED therapy reduces the risk of SUDEP [19].

SUDEP is primarily a sleep-related and unwitnessed phenomenon [14]. Most studies reported that only 10% of deaths were witnessed, usually in association with

GTCS [13, 14]. Another study on SUDEP among patients with learning disabilities found that all 14 deaths occurred while the patients were unsupervised and unobserved [20]. Some of the early studies on SUDEP reported that around 50% of patients were found dead in bed and the majority were in the prone position [21, 22]. Additionally, in the MORTEMUS study, “most patients had their face slightly tilted to the side and not strictly down the pillow” [17]. More recently, a systematic review found a significant association between SUDEP and the prone position with 73.3% deaths in the prone position, and the prone position was significantly more frequent in younger patients (age < 40 years) [23].

## Pathophysiology

The pathophysiology of SUDEP is complex and the exact mechanism of death is not well established. However, several potential factors have been postulated based on observations in humans with SUDEP and animal experiments. Seizure-related respiratory dysfunction, cardiac abnormalities, dysfunction of the autonomic nervous system and postictal cerebral dysfunction (‘cerebral shutdown’) are considered to be the most important mechanisms. At cellular level, serotonin deficiency and activation of adenosine receptors have been found to be important contributors [24]. Genetic susceptibility has also been postulated as a potential mechanism. Certain genes are expressed in both the brain and the heart. Two such genes, *KCNA1* and *SCN1A*, have been linked to SUDEP [24]. It is likely that multiple mechanisms contribute to SUDEP in a given individual [24].

Seizure-induced respiratory dysfunction is considered to be a major potential mechanism. Studies have shown hypoventilation, apnoea, hypoxia and hypercapnia during seizures [24]. The association between the prone position and SUDEP is significant in this context. Under normal circumstances, arousal and repositioning is likely to occur in this situation. In the MORTEMUS data, it was noted that patients who died of SUDEP remained in the same prone position until death [17]. This observation raises the possibility of suppression of the brainstem arousal centre as a contributory factor. Serotonergic neurons play an important role in the arousal system and the breathing centre in the brainstem, and suppression of serotonergic activity could be an important underpinning mechanism [25]. Animal models have provided evidence supporting serotonin dysfunction as a mechanism of SUDEP [26].

Cardiac dysfunction and dysrhythmias secondary to seizures and hypoxia are likely to be contributory mechanisms [24]. In the mouse model of Dravet syndrome, ictal bradycardia lead to SUDEP [27]. Decreased heart rate variability due to autonomic dysregulation has also been postulated as a potential mechanism [24].

## Prevention

At present, no robust conclusions can be drawn about interventions to prevent SUDEP as the underlying pathophysiologic mechanisms have not been clearly identified. However, case-control studies and observational studies have yielded useful information on risk factors. Interventions to modify such risk factors provide an opportunity to prevent or reduce the risk of SUDEP.

The frequency of GTCS is the most consistent and important risk factor defined in case-control studies [12]. Hence, improving seizure control is likely to be an ideal intervention to mitigate the risk of SUDEP. Achieving seizure freedom should be the goal with the appropriate use of AED therapy, epilepsy surgery, ketogenic diet, and other interventions such as neurostimulation, including vagal nerve stimulation. It should be stressed to patients that poor compliance with AED therapy increases the risk of SUDEP [28]. A meta-analysis of randomised trials has shown that adjunctive AED therapy reduced the risk of SUDEP by more than sevenfold [19].

Seizure alarms and supervision at night are potential interventions to prevent seizure-related hypoxia by repositioning and inducing arousal [29]. Studies indicate that the vast majority of SUDEP cases are unwitnessed [13, 14, 17], suggesting supervision and early intervention may be helpful in prevention. Early nursing interventions such as supplemental oxygen administration, oropharyngeal suction, and patient repositioning have been found to shorten the duration of seizure-related respiratory dysfunction [30]. Selective serotonin reuptake inhibitors (SSRI) have been found to be effective in reducing respiratory dysfunction in the mouse model of SUDEP [26]. Patients on SSRI treatment had reduced severity of seizure-related oxygen desaturation during focal seizures, but there is insufficient human data and the value of SSRI in preventing SUDEP remains speculative at present [31].

Ictal cardiac arrhythmias can be secondary to hypoxia or autonomic cardiac effects of seizures. Hence, prevention of respiratory dysfunction is of importance to minimise cardiac effects. The place of pacemaker or automatic cardioverter-defibrillator implantation to reduce the risk of SUDEP is unclear [24]. Early administration of oxygen during seizures has been found to prevent PGES [32]. Similarly, early nursing interventions including oxygen administration during seizures appear to shorten the duration of PGES [30]. So, early peri-ictal interventions such as oxygen administration, oropharyngeal suctioning and repositioning of the patient may be helpful in preventing SUDEP.

### Current clinical practice versus patient expectations

Whether all patients with epilepsy should be routinely informed of SUDEP is a matter of discussion and debate

[33]. There is no consensus on the optimal way of communicating the risk of SUDEP to patients and caregivers [34]. National Institute for Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) in the United Kingdom recommend disclosure of adequate information on SUDEP to every patient, their family or caregivers as a requisite of good practice [35]. The American Epilepsy Society and the Epilepsy Foundation Joint Task Force on SUDEP have similar recommendations [36]. Despite these recommendations, the actual clinical practice varies considerably. According to a study, only 5% of the UK neurologists discussed SUDEP with every patient [37]. A survey of American neurologists found that 35% of neurologists never discussed SUDEP with their patients [38]. A recent survey from a tertiary centre found poor awareness of SUDEP among adult patients with epilepsy. Nevertheless, the majority (89.5%) wished to be informed about SUDEP, and 59% requested detailed information. The treating neurologist was considered to be the most appropriate source of SUDEP information by 85.6% of patients [35]. These data indicate the need for improving awareness and the importance of discussing about SUDEP with patients.

## Conclusions

SUDEP is associated with serious consequences on families and a considerable burden on health care systems. Case-control studies have identified several risk factors, though exact mechanisms of SUDEP have not been well identified. Frequent GTCS, nocturnal seizures, and prone position are among the most important risk factors. Currently, modification of those risk factors remains the most practical intervention to reduce the risk of SUDEP. There is a need to increase awareness of SUDEP among the general public, patients, policy makers and health care providers.

## Conflicts of interests

There are no conflicts of interest.

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