Summary

Sudden Unexpected Death in Epilepsy (SUDEP) is one of the most frequent causes of death among patients with drug resistant epilepsy, primarily affecting young adults between 16 and 45, with frequent generalized tonic-clonic seizures. This review summarizes current knowledge about SUDEP, its true risk and potential prevention, as well as recent practice guidelines for better informing patients and caregivers.

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Introduction

SUDEP is a non-accidental, non-suicidal and non-drowning death in people with epilepsy, unrelated to a documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death [1]. SUDEP represents one of the main concerns of the epilepsy community, in as much as this outcome typically affects young adults between the age of 16 to 45 [2]. The incidence of SUDEP in epilepsy is 27 times higher than sudden unexpected death in other populations [3], part of it explained by comorbidities, but even when adjusted for it, the risk is three fold higher for patients with epilepsy. Most of these young adults do not suffer from other serious conditions than seizures and neither their family nor theyselves are usually aware of the risk of SUDEP, making this event as devastating as the sudden cardiac deaths observed in the same age group. The age range of SUDEP occurrence also accounts for such death to represent the second leading neurological cause of total years of potential life lost, after stroke [4]. Patients with epilepsy are at high risk of premature mortality [5, 6]. Focal and generalized tonic-clonic seizures are the most common cause of death among children and adults with epilepsy [6, 7]. However, other seizure types, anti-seizure therapies, and comorbid disorders can also increase mortality. For many epilepsy populations, SUDEP is the principal cause of death [4]. Patients with epilepsy also have increased mortality compared with control populations, due to status epilepticus, motor vehicle accidents, falls, drowning, suicide, drug poisoning, assault, and pneumonia [5, 6]. SUDEP and other causes of epilepsy-related mortality are an enormous public health problem.

Overall, one SUDEP occurs every 10 minutes worldwide. The incidence for SUDEP risk is estimated to 0.22/1000 patient/years in children and 1.2/1000 patient/years in adults with epilepsy [8]. In patients with drug-resistant epilepsy, SUDEP incidence is about 0.5% [2], culminating to 0.93% in patients undergoing presurgical evaluation or having failed epilepsy surgery [9]. The main SUDEP risk factor currently known is the
presence of generalized tonic-clonic seizures (GTCS), with an odd-ratio of 19.1 (11.8 - 31.0) for patients with ≥ 3 GTCS/year as compared to those with no GTCS [10]. However, these data derive from retrospective case-controlled studies performed in population with lower SUDEP incidence than surgical cohorts, i.e. 0.1% and 0.2% [11]. Considering that 12% of patients had ≥ 3 GTCS/year [12], crude extrapolations suggest that the risk of SUDEP in such patients shall be around 1%/year (i.e. comparable to the highest figure described in epilepsy surgery cohorts) [9].

The incidence of SUDEP is very low in children with epilepsy [3]. However, certain types of childhood epilepsy, such as Dravet syndrome, put patients in the high risk category for developing SUDEP [13]. Surprisingly, a few SUDEP were recently reported in benign childhood epilepsy with centro-temporal spikes (BECTS), maybe due to the fact that patients are often not treated with antiepileptic drugs [14]. After 40 years of follow-up, up to 20% of patients with childhood-onset epilepsy and no terminal 5-year remission will have died of SUDEP [15, 16]. Thus, while SUDEP remains a rare event for doctors, it represents a very significant risk for patients suffering from refractory seizures since childhood.

There is an increase interest in this topic over the last few years – just in 1995 there were less than 10 papers published using the term “SUDEP”; since 2013 there are more than 60 papers indexed in pubmed for the search term “SUDEP” per year [17]. Although the interest for SUDEP is increasing, data shows that a significant proportion of general practitioners, especially pediatricians, are unaware of the true risk of SUDEP [18].

**Classification of SUDEP**

SUDEP can be categorized as following [1, 19, 20]:

1. **Definite SUDEP** – cases in which death occurs in a relatively healthy person (apart from epilepsy).
2. **Definite SUDEP Plus** – cases that would otherwise fulfill the definition of SUDEP, when evidence indicates that a preexisting condition, known before or detected after autopsy, might have contributed to the death, which otherwise would be classified as SUDEP.
3. **Probable SUDEP** – cases that are similar to definite SUDEP, but the postmortem data is not available.
4. **Near-SUDEP** – cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than 1 hour.
5. **Possible SUDEP** – when there is a competing cause of death, with insufficient data available to allow their attribution to this category. Death occurring in water, without circumstantial or autopsy evidence of submersion are also categorized here. If any evidence of submersion is present, the death should not be classified as SUDEP.

**Mechanisms of SUDEP: Role of post-GTCS dysfunction of brainstem respiratory centers**

Most SUDEP are unwitnessed, limiting our understanding of their underlying mechanisms. In the minority of witnessed seizures, SUDEP seems to be usually triggered by a generalized tonic-clonic seizure (GTCS) [2, 11, 21 - 24]. Exceptions to this rule have been scarcely reported [25], and might include rare gene mutations which might affect heart, lung, and brain (SCN1A, SCN2A, SCN5A, SCN8A, NOS1AP, DEPDC5, CSTB, TSC1, TSC2, HCN2, HCN4, KCNQ1, KCNH2, NOS1AP, RYR2) [24].

Our current understanding on how GTCS leads to SUDEP primarily derives from the rare monitored cases of patients who died of a SUDEP while undergoing in-hospital video-EEG recording of their seizures within the context of pre-surgical evaluation of their drug-resistant epilepsy. The MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) tackled this issue by organizing a worldwide survey of SUDEP and near-SUDEP captured in EMUs [23]. This research included 16 SUDEP cases and nine near SUDEP cases. The study showed that all monitored SUDEP occurred after a GTCS with a sequence characterized by: 1) a seizure usually occurring at night in an unsupervised patient sleeping in the prone position, 2) the presence of polypnea and tachycardia at the end of the GTCSs, together with severe post-ictal EEG flattening, 3) the abrupt development of concurrent apnea and bradycardia or asystole between 30 seconds and three minutes post-ictal, 4) immediate death following this early cardiorespiratory arrest, or transient restoration of abnormal respiration and EKG during several minutes, leading to terminal apnea followed by terminal asystole. Importantly, patients dying of SUDEP do not seem to develop physiological reactions to counteract their prone position and trigger autoresuscitation. Even though the patients are found in the prone position, the face is usually tilted and the airways are not completely obstructed, and the witnessed cases of SUDEP indicate that patients experience breathing difficulty [31].

Interpretation of this sequence of events remains partly speculative. Apnea is already present during GTCS, and might be responsible for significant hypoxemia in some cases, contributed to by the prone position and ventilation-perfusion inequality [32, 33]. When GTCS ends, hypoxemia might account for both the polypnea and EEG suppression. However, an additional mechanism occurs within the next three minutes to account for the abrupt cardiorespiratory dysfunction. Seizures are known to trigger the release of endogenous opioids and adenosine within the brain and brainstem, a mechanism thought to participate to seizure termination. This release of endogenous depressors may exacerbate the impact of GTCS-induced hypox-
emia upon brainstem activities, eventually resulting in the sudden breakdown of cardiorespiratory functions observed in MORTEMUS. This would lead to immediate death or to further alterations of brain and brainstem oxygenation reflected by ineffective respiration until terminal apnea. While supported by a large bulk of evidence, MORTEMUS study did not provide direct variation of the respiratory functions, such as changes in pH, pCO2 and pO2. Near-SUDEP cases indicate the prevalent role of post-ictal apnea [34]. The later, the possible link between SUDEP and postictal generalized suppression of EEG could serve as a marker of SUDEP [26].

MORTEMUS has described monitored SUDEP cases, however, about 80% of all SUDEP are unwitnessed [35], suggesting that witnessed GTCS are less likely to end up as sudden deaths. That might also be the case for GTCS in children, where parental supervision is prevailing, thus reducing the probability to end up as SUDEP.

The large majority of data obtained in animal models of SUDEP are in line with some of the above hypothesis and human observations. Indeed, DBA/1 and DBA/2 audiogenic seizure mice, as well as knockout mice for 5-HT2c, Kcnal1, Scn1a and RyR2 genes, or with genetic deletion of serotoninergic neurons, all display a pattern whereby seizures will lead to postictal apnea and death [7, 24, 36, 37]. A similar mechanism was observed after bicuculline-induced seizures in sheep [38]. In some of these models, a seizure-triggered spreading depression in the brainstem appears to drive the respiratory and cardiac dysfunction leading to death [36, 37]. In another model, apnea and death were promoted by seizure-triggered adenosine release, and partly reversed with caffeine [39]. SUDEP was also prevented in DBA/2 mice by injection of selective serotonin-recapture inhibitor [40].

Risk factors for SUDEP

The most frequently described risk factor for SUDEP is the presence of GTCS. This is aggravated by an early onset of epilepsy and long history of epilepsy [41]. Presence of frequent GTCS (≥ 3 GTCS per year) increases the risk of SUDEP 15 times [42]. There are also risk factors that are potentially modifiable: poor adherence to antiepileptic medication, sub-therapeutic medication levels, alcohol consumption, lack of night surveillance, sleeping in the prone position and increase in seizure frequency [43].

Prevention of SUDEP

There is no treatment specific for SUDEP. Currently, the only treatments that might provide some protection against SUDEP are those aiming at reducing the frequency of GTCS [19]. There is thus an urgent need to make progress in SUDEP prevention.

There are a number of measures that are being proposed to reduce the occurrence of SUDEP, such as...
compliance to the treatment plan, adequate treatment – especially in patients with GTCS, optimal dosage of antiepileptic drugs, use of lattice pillow and nocturnal supervision in patients with poorly controlled seizures. However, none were firmly proven to be effective. Regarding pharmacological treatments, there is a rationale for testing the impact of selective serotonin reuptake inhibitors (SSRI), as well as opiate- or adenosine inhibitors [44].

**Recommendations**

Neurologists are facing the challenge of whether to disclose the information about the risk of SUDEP. Only 4 to 6.8% of clinicians discuss this topic with their patients [45, 46]. Studies show that patients and parents of a child with epilepsy are more inclined to hear about the risk of SUDEP from their treating physician [47, 48]. Practice guidelines were recently published by the American Academy of Neurology [8], suggesting that clinicians should inform adult patients and parents of a child with epilepsy that: 1) SUDEP is a rare, yet possible outcome (1 in 1000 in adults and 1 in 4500 in children per year); 2) the presence of frequent GTCS is an important risk factor that should prompt optimal medical management, keeping the balance between benefits and risks of new therapeutic approaches; 3) seizure freedom is associated with a lower risk of SUDEP; and 4) when possible, nocturnal supervision is recommended, especially for patients with GTCS [8].

**References**

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