Prevention of sudden unexpected death in epilepsy: current status and future perspectives

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1

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Abstract

Introduction:

Sudden unexpected death in epilepsy (SUDEP) affects about 1 in 1000 people with epilepsy, and even more in medically refractory epilepsy. As most people are between 20 and 40 years when dying suddenly, SUDEP leads to a considerable loss of potential life years. The most important risk factors are nocturnal and tonic-clonic seizures, underscoring that supervision and effective seizure control are key elements for SUDEP prevention. The question of whether specific antiepileptic drugs are linked to SUDEP is still controversially discussed. Knowledge and education about SUDEP among healthcare professionals, patients and relatives are of outstanding importance for preventive measures to be taken, but still poor and widely neglected.

Areas covered:

This article reviews epidemiology, pathophysiology, risk factors, assessment of individual SUDEP risk and available measures for SUDEP prevention. Literature search was done using Medline and Pubmed in October 2019.

Expert opinion:

2

Significant advances in the understanding of SUDEP were made in the last decade which allow testing of novel strategies to prevent SUDEP. Promising current strategies target neuronal mechanisms of brain stem dysfunction, cardiac susceptibility for fatal arrhythmias, and reliable detection of tonic-clonic seizures using mobile health technologies.

Keywords:

Epilepsy, sudden death, antiepileptic drugs, lamotrigine, tonic-clonic seizures, prevention, premature mortality, seizure detection devices

Abbreviations:

AED, antiepileptic drug; CBZ, carbamazepine; cLQTS, congenital long QT syndrome; EMU, epilepsy monitoring unit; FBTCS, focal to bilateral tonic-clonic seizures; GTCS, generalized tonic-clonic seizures; ICA, ictal central apnea; LTG, lamotrigine; PCCA, postconvulsive central apnea; PGES, postictal generalized EEG suppression; SRI, serotonin reuptake inhibitor; SUDEP, sudden unexpected death in epilepsy; TCS, tonic-clonic seizures

1. What is SUDEP?

According to the most recent definition, SUDEP is considered as the sudden and unexpected death of a person with epilepsy which occurs under benign circumstances and which is not due to drowning, intoxication, injury or other internal or external factors [1] (see table 1). Signs of a preceding seizure may be present or not. If a postmortem examination does not reveal an alternative cause of death, this confirms "definite SUDEP". Cases in which potentially lethal alternative causes are excluded, and otherwise all criteria are met, but an autopsy lacks, are categorized as "probable SUDEP". The term "possible SUDEP" describes scenarios in which other fatal causes cannot be ruled out. Similarly, the expression "SUDEP plus" is used when a patient also suffered from other diseases that may have caused the death, but there are no clues that the alternative condition has truly caused it. Cases in which cardiopulmonary resuscitation prevented the lethal course are called "near-SUDEP". A fatal status epilepticus lasting more than 30 minutes prior to death is not considered as SUDEP.

2. How frequent is SUDEP and in whom does it occur?

People with epilepsy have an increased risk of premature death compared to the general population [2]. SUDEP incidence rates were currently estimated and amounted to 0.58 per 1000 patient years over all age groups, 0.22 in children and adolescents, and 1.2 in adults. In other words, about 1 out of 1000 adults and 1 out of 4500 children with epilepsy is dying from SUDEP per year [3]. More recent data, however, suggest considerably higher incidence rates for children and adolescents, resembling those of adults [4]. While pediatric specific risk factors are not well understood yet [5–7], epidemiological studies identified the following risk factors in adults: Younger age (24-fold increased risk of SUDEP in the age group between 20 and 40 years), male sex, early onset epilepsies, focal onset epilepsies, intellectual disability, insufficient compliance

to therapy and insufficient seizure control [8–16]. The SUDEP risk varies with the severity and the response to treatment, and especially people with difficult-to-treat epilepsies and potential candidates for epilepsy surgery have an elevated SUDEP risk as compared to people with well controlled epilepsies or conditions considered as benign [17]. However, SUDEP also occurs in patients early in the disease course, who are thought to be treatment responsive or to have benign epilepsies [18,19]. Nocturnal seizures and tonic-clonic seizures (TCS), i.e. generalized tonic-clonic seizures (GTCS) and focal to bilateral tonic-clonic seizures (FBTCS), were identified as the most important risk factor with a strong correlation between the patients' SUDEP risk and the number of TCS per year [3,10,11,20].

3. What are the events and mechanisms leading to SUDEP in most cases?

Most SUDEP cases are unwitnessed [11,19], and thus the events leading to death were unknown for centuries. A historical note on a witnessed case already pointed towards a relationship between seizure activity and SUDEP. George Washington, the first President of the United States, was present when his 17-years old stepdaughter Patsy Custis died suddenly and unexpectedly in 1773. He described the situation as follows: "She rose from dinner […] in better health and spirits than she appeared to have been in for some time; soon after which she was seized with one of her usual fits, and expired in it, in less than two minutes without uttering a word, a groan, or scarce a sigh." [21].

Indeed, most witnessed SUDEP cases occurred in the aftermaths of a TCS [22,23]. A milestone in the understanding of the lethal events is the MORTEMUS study, a worldwide effort to collect and review SUDEP cases that occurred in epilepsy monitoring units (EMUs) [24]. In EMUs, patients are continuously supervised by video, EEG, one-lead ECG and sometimes pulse oximetry, while AEDs are reduced or completely withdrawn, in order to facilitate and record

seizures for diagnostic reasons during the patient's time of stay. Ryvlin and colleagues collected 29 cases of cardiorespiratory arrest in EMUs, of which 16 were classified as definite SUDEP (14 of them occurring at night), 9 as near SUDEP (mostly occurring at daytime) and 4 as alternative cause of death. In line with TCS as the most important risk factor, all analyzed SUDEP cases occurred in association with FBTCS. Continuous monitoring data were available in ten SUDEP cases, revealing a rather uniform cascade of cardiorespiratory dysfunction. In the early postictal phase, a transient tachypnea for about 3 minutes was followed by (partly fluctuating) abnormal breathing patterns, including sustained periods of apnea. In some instances, the onset of these patterns was delayed to up to 11 minutes after seizure termination. During these apneic periods, patients developed bradycardia that resulted in terminal asystole after a further 1 to 3 minutes. As a characteristic EEG pattern in the postictal phase, a generalized flattening of amplitudes was identified in all monitored SUDEP cases, putatively reflecting an overall suppression of brain activity (postictal generalized EEG suppression, PGES). Altogether, this fatal cascade leading to SUDEP was labelled as "neurovegetative breakdown" by the authors of the study (see also figure 1).

Postictal generalized EEG suppression

In the aftermath of non-fatal TCS, surface EEG displays PGES in about 50% of the cases [25,26]. PGES occurs more frequently in TCS arising from sleep, with a longer tonic phase, bilateral tonic extension of the upper limbs and oral tonicity [26–29]. A seminal case-control study suggested that prolonged PGES is a predictor of SUDEP [30]. This finding, however, was not replicated in a subsequent study, and PGES was shown to occur inconsistently in individuals, challenging its value as a marker of an elevated SUDEP risk [25,31]. Instead, PGES appears to be a marker of peri-ictal hypoxemia, and simple interventions to stimulate arousal or respiration

as well as early administration of oxygen shorten both hypoxemia and PGES [27,32–34]. Postictal immobility and duration of PGES are linked to severity of hypoxemia [35]. However, hypoxemia or postictal immobility were not more common after TCS arising from sleep, suggesting that there are no particularly sleep-related mechanism facilitating SUDEP, but rather the fact that nocturnal seizures are more likely to be unobserved [28]. The underlying mechanisms related to PGES are still unknown, and studies using scalp and intracranial EEG recordings challenge the view that PGES as assessed by surface EEG consistently reflects general suppression of brain activity [36,37]. Data from animal models, however, suggest that PGES occurs in association with a seizure-linked depolarization wave which can ultimately spread from cortical areas to the brain stem [38], thereby suppressing neurons which drive cardiorespiratory function. In conclusion, PGES appears a necessary, but not a sufficient condition for the neurovegetative breakdown in TCS-related SUDEP, as in the aftermath of most TCS with PGES, neuronal activity and the EEG signal returns back to normal states.

Seizure-related respiratory dysfunction and deficits in serotoninergic signaling

Seizure-related respiratory disturbances with transient hypoxemia and hypercapnia occur in 33-43% of focal seizures [39–41], mostly due to central or obstructive apnea. Ictal central apnea (ICA) occurs in one third of seizures with focal onset and 43% of patients, especially when arising from sleep and from temporal lobes; the recurrence risk in a given patient amounts to 75%. Postconvulsive central apnea (PCCA) occurs in one fifth of TCS with focal or generalized onset and 22% of patients, especially in women; the recurrence risk in a given patient amounts to 53% [42]. PCCA is considered as a possible biomarker for SUDEP, as in a recent case series it was reported in association with asystole in two cases and in one person who later died of

SUDEP [43,44]. In this context, CO_2-dependent arousal mechanisms and serotonin signaling are also discussed to contribute to the fatal cascade [45]. Increased levels of serotonin are thought to inhibit seizures and some AEDs may at least partially exert their clinical effects via enhancing extracellular serotonin [46]. Importantly, serotoninergic neurons in the brain stem have an impact on many different functions and networks in the brain, among others on arousal and control of breathing. Data from animal models suggest that postictal deficits in serotoninergic signaling could lead to or aggravate hypoventilation and impair arousal reaction to postictally elevated CO_2 levels [46]. For instance, in DBA/1 and DBA/2 mouse models with audiogenic reflex-seizures and subsequent respiratory arrest, administration of serotonin reuptake inhibitors (SRIs) prevented respiratory arrest [47] and 5HT2c-receptor knockout-mice often die after seizure-related apnea, indicating the relevance of serotoninergic neurons in the development of central apneas [48]. In humans, postmortem analysis of the ventrolateral medulla, especially of the pre-Bötzinger complex and the medullary raphe nuclei showed greater reductions of neuron populations and neuromodulatory neuropeptidergic and mono-aminergic systems involving serotonin and galanin in SUDEP patients as compared to controls [49]. Furthermore, blood serotonin levels were found to be elevated after seizures without ICA or PCCA, but not after seizures with ICA or PCCA [50]. Likewise, duration of PGES was inversely correlated with interictal serotonin blood levels, prompting the hypothesis that blood serotonin levels play a role in shaping seizure features or may partly reflect serotonin levels in the CNS [51]. The hypothesis that serotonin levels have an impact on seizure features is further supported by the observation that patients taking SRIs display less frequently ICA, and patients on chronic treatment with benzodiazepines have shorter ICA and PGES durations [52,53].

Recently, possible associations between obstructive sleep apnea and SUDEP risk were also discussed [54]. In addition to that, epileptic seizures, particularly GTCS and FBTCS with a duration of more than 100 seconds, can lead to clinically unapparent neurogenic pulmonary edema, most likely due to a massive seizure related release of catecholamines [55,56]. Accordingly, post-mortem examinations of SUDEP patients showed signs of pulmonary edema in 62% of the cases [57,58].

Altogether, these observations suggest that postictal respiratory dysfunctions occur frequently, but that the fatal cascade leading to SUDEP is fortunately rare. People with nocturnal seizures, and thus seizures occurring during sleep, are at higher risk for SUDEP [11]. Therefore, it is not surprising that affected patients are frequently found dead in bed in the morning. Intriguingly, SUDEP patients are mostly found in prone position, which indirectly implies a mechanically more difficult and less effective respiration [24,28,59].

4. SUDEP and sudden cardiac death – two overlapping entities?

The majority of monitored SUDEP cases result from a primary postictal apnea followed by bradycardia and asystole within minutes after seizure termination [24]. In line with this finding, potentially arrhythmogenic ECG changes were observed in a minority of seizures only during conventional EMU recordings [60–63]. However, in about 0.4% of patients during video-EEG monitoring ictal bradycardia and asystole occur, which was in all cases self-limiting and most probably due to activation of vasovagal reflex pathways or impaired balance between sympathetic and parasympathetic branches of the autonomic nervous system [64]. Since ictal bradyarrhythmias may lead to syncopes and falls, a treatment with cardiac pacer devices is recommended in these cases if full seizure control cannot be achieved [64–66]. A small and maybe underestimated portion of SUDEP cases is caused by peri-ictal ventricular arrhythmias,

some in the context of a Takotsubo cardiomyopathy, as described in a number of case reports [67–72]. Ventricular tachycardias, in turn, are facilitated by abnormalities of cardiac repolarization (e.g. prolonged QT intervals, increased QT dispersion, increased T wave alternans) which are commonly found in people with chronic epilepsy [73,74]. Valid ECG predictors for an increased SUDEP risk, however, were not convincingly reported to date [62,75].

Epileptic seizures commonly lead to sinus tachycardia, partially in reaction to considerably elevated release of catecholamines [64,76]. In this context, it is important to note that elevated levels of troponin were detected in 25% of non-fatal GTCS and FBTCS in people with epilepsy but without cardiac disease, and that troponin levels were positively correlated with dopamine levels [76]. This suggests that even non-fatal TCS can lead, via repetitive surges of catecholamines, to subtle cardiac damage which may have a cumulative detrimental long term effect, utlimately leading to an 'epileptic heart'. Indeed, some patients with epilepsy (and status-epilepticus) display alterations of the cardiac ventricles, such as fibrotic remodelling and contraction band necrosis, with potentially arhythmogenic effects [77,78]. In SUDEP patients, structural changes of heart muscle tissue are no more frequent than in other epilepsy patients [79], yet it seems plausible, that a fraction of sudden deadly events in epilepsy patients are due to sudden cardiac death irrespective of a neurovegetative breakdown, resulting in a partly overlap of sudden cardiac death and SUDEP [80]. This hypothesis is also supported by the fact that a sizeable (about 10%) portion of SUDEP cases happened in the absence of apparent seizure activity [22,81]. At the same time, SUDEP cases that are caused by a primary seizure related apnea and a secondary asystole, are sometime missdiagnosed as sudden cardiac deaths [82]. Interestingly, a significant proportion (about 20%) of SUDEP-cases have a genetic predisposition

for cardiac arrhythmias [83]. In view of the phenomenological similarity between SUDEP, sudden cardiac death and sudden infant death syndrome, extensive human genetic testing has been performed and some overlap has been found. Gene variants in potassium channels (KCNA1 in SUDEP, KCNQ1, KCNH2 in long QT syndrome, sudden infant death and SUDEP) and sodium channels (e.g. SCN1A in SUDEP and sudden infant death, SCN2A, SCN8A in SUDEP, SCN5a in sudden cardiac death and sudden infant death) were recently described [84]. Some genetic epilepsy syndromes such as Dravet syndrome (especially SCN1A mutations), Ohtahara syndrome (SCN2A), and early infantile epileptic encephalopathy (SCN2A, SCN8A) variants appear to be particularly prevalent in SUDEP [84,85].

In addition to cardiac mechanisms, alterations of systemic blood pressure may contribute to SUDEP in some cases [86]. For instance impaired sensitivity of baroreceptors and altered regulations of blood pressure may facilitate transient postictal hypotension, possibly influencing the development of SUDEP alongside respiratory and cardiac dysfunctions [87,88].

5. How do neuroimaging studies contribute to the understanding of SUDEP?

Structural and functional imaging studies in the context of SUDEP research show changes of regional brain structure and of networks involved in respiratory, cardiovascular and central autonomic control [89,90]. Voxel-based morphometry revealed reduced gray matter volume of the posterior thalamus in SUDEP patients and in people at elevated risk [91,92]. The posterior thalamus is thought to be involved in breathing control [93,94], and volume loss in this region, particularly in the pulvinar, is a common observation in patients with obstructive sleep apnea [95], heart failure [96] as well as GTCS and FBTCS [97–99]. Furthermore, in patients with GTCS and FBTCS, widespread cortical thinning in frontal and parietal areas [100,101] as well as

local cortical thickening [101] is reported. For the cortical thinning, a huge overlap was detected in patients with or at high risk of SUDEP and those who showed PGES in EEG [102]. In SUDEP patients, a recent study also showed volume loss in areas related to cardiorespiratory recovery, such as the medulla oblongata [103] as well as the cerebellum and the periaqueductal grey, accompanied by enhanced tissue thickness in areas that may be involved in triggering apnea or hypotension, such as the amygdala and the subcallosal cortex [92].

6. What can be done to reduce the SUDEP risk?

6.1 Risk assessment

Despite increasing insights into the pathophysiology of SUDEP, reliable biomarkers and unequivocal predictors of SUDEP are still lacking [104]. Nonetheless, well known clinical risk factors can help to establish measures to prevent and counteract SUDEP. A substantial number of risk factors are, at least in principle, modifiable including frequency of TCSs, nocturnal seizures, unsupervised night sleep and treatment adherence issues [105]. Importantly, the concomitant presence of selected risk factors dramatically increases the danger, e.g. people with TCSs who sleep alone have a more than 67-fold increased SUDEP risk [106]. It appears plausible that a regular assessment of risk factors using safety checklists [106,107] and that communication and information about premature mortality and its causes are likely to improve the management and mitigation of individual SUDEP risks. Indeed, specialized epilepsy care with a wide range of diagnostic and therapeutic options has proven to lower premature mortality [108], underscoring the benefits of advanced skills and comprehensive care of people with epilepsy.

6.2 Prevention by seizure control

The most important risk factor for SUDEP is a high frequency of TCSs [17,23,109–111] and it has been shown that adding an effective AED treatment in patients with uncontrolled seizures can reduce the risk more than seven times [112]. Thus, the administration of an appropriate AED treatment regimen for individual patients and adherence to the treatment are of outstanding importance to mitigate the SUDEP risk. It is, however, controversially discussed whether specific AEDs are associated with an elevated risk of SUDEP and which AEDs may be appropriate for a given constellation.

6.2.1 Pharmacological control of GTCS in generalized genetic epilepsies

It has been well known for decades that AEDs can work differently when used in generalized epilepsy compared to focal epilepsy [113]. Therefore, scientific trials examining the efficacy and safety of AEDs have commonly been carried out either in patients with focal epilepsy or in patients with generalized epilepsy, avoiding a mixture of generalized and focal epilepsies in the same study [114–116]. In studies on possible associations between the use of specific AEDs and SUDEP, however, this knowledge has largely been neglected [8,10,117–119]. Furthermore, an increased vulnerability to drug induced cardiac arrhythmia may be present in an unknown proportion of individuals with generalized genetic epilepsy (formerly called idiopathic) as there is an overlap between cardiac and neuronal channelopathies [120,121]. Increasing evidence suggest that the congenital long QT syndrome can be associated with not only malignant arrhythmias but also genuine epilepsy [121–127] and individuals with congenital long QT syndrome can be put at risk if treated with ion channel blockers increasing the risk of cardiac arrhythmia [128]. Alterations of cardiac repolarization are not uncommon in TCSs [62], and if a patient in addition to having a GTCS has a cardiac channelopathy and is being treated with an ion channel blocker, the risk of a fatal arrhythmia may be particularly increased.

The discussion whether individual AEDs can influence the risk of SUDEP was initiated in 1998 when Timmings reported a cohort with a significantly higher proportion of SUDEP victims on carbamazepine (CBZ) (85%) compared with the proportion on CBZ in controls (38%) [117]. Drug-induced cardiac arrhythmia was suggested as a possible explanation. However, the possibility that the findings could be due to the use of CBZ in patients that could risk an inferior seizure protection was not discussed. Five years earlier the same cohort of SUDEP victims had been described by the same author and 10 of the 14 SUDEP victims had generalized genetic epilepsy [129]. Many AEDs are ion channel blockers and can show inferior efficacy when used in generalized genetic epilepsy. CBZ, lamotrigine (LTG) and phenytoin can even cause seizure deterioration [130–132].

However, among the several AEDs on the market only CBZ and LTG have been suggested to play a possible role in the causation of SUDEP. LTG inhibits the cardiac rapid delayed rectifier potassium ion current Ikr, and many drugs with the same ability have been associated with syncopes and sudden deaths, and have therefore been excluded or withdrawn from the market [133–135]. In 2007, based on a series of four SUDEP cases that all were females with generalized genetic epilepsy who had been treated with LTG in monotherapy, it was discussed whether this clinical experience was due only to coincidence [136]. Alternative explanations could be inferior efficacy when used in generalized genetic epilepsy or a drug induced terminal cardiac arrhythmia in (genetically) vulnerable individuals, as it is known that female patients are at a higher risk of drug-induced torsade de pointes arrhythmias than men [137,138]. A systematic study then showed a significantly higher proportion of female SUDEP victims on LTG than the proportion in female controls. Furthermore, the incidence of SUDEP in females on LTG was

estimated to be 2.5 per 1,000 patient-years compared to 0.5 per 1,000 patient-years in female patients with epilepsy who were not treated with LTG [139].

These findings were in line with the results from the largest study that so far has been conducted on AEDs and SUDEP [140]. The study which was conducted by the ILAE Commission on Epidemiology, Subcommission on Mortality, included 289 SUDEP victims from four different countries. It demonstrated a significantly increased risk of SUDEP in patients with generalized genetic epilepsy who had been on LTG, but not even a tendency to an increased risk in patients with focal epilepsies. Intriguingly, when the same data were analyzed in a subsequent study without stratification according to the epilepsy types, it was concluded that LTG has no impact on the SUDEP risk, but that only the frequency of TCS matters [10]. The conclusion of the subsequent study that LTG has no impact on the SUDEP risk is rather debatable for several reasons: The epilepsy subgroups were not considered separately, so that the significant effects of smaller subgroups (i.e. patients with generalized genetic epilepsies on LTG) were 'diluted'. After correcting for the frequency of TCSs there was no longer evidence of an increased frequency of SUDEP in patients on LTG. However, the risk in females on LTG monotherapy was 6.6 times higher than in females not on LTG [10, 139]. The difference was not statistically significant, and therefore it was concluded that there is no difference. However, the confidence interval was very wide (0.3-174.9) consistent with an interpretation suggesting that a subgroup of individuals may have been at increased risk. Since the individuals with generalized genetic epilepsies were not examined separately, no conclusion regarding the use of LTG in this particular subgroup of patients can be drawn. Furthermore, one could question whether a statistical correction for seizure frequency is adequate when studying possible associations between AEDs and SUDEP, since this will eliminate differences in efficacy between AEDs. In generalized genetic epilepsies

LTG has inferior efficacy compared to valproate [141,142], and when using an AED with inferior protection against GTCSs, one could expect a higher occurrence of SUDEP. SUDEP occurs primarily in the context of a GTCS. Correcting for the frequency of GTCSs could answer the question whether there is a difference in the proportion of SUDEP victims on LTG compared with patients not on LTG, independent of the occurrence of GTCSs - which is when SUDEP occurs. The most important factor for SUDEP has then not been considered. In a further meta-analysis of randomized controlled trials with LTG, SUDEP rate of patients on LTG was not statistically different as compared to those on placebo or other active AEDs. This meta-analysis only comprised a rather small group of patients with generalized genetic epilepsy with no SUDEP event in this group, limiting its value for the question of whether LTG increases the SUDEP risk of women with generalized genetic epilepsies. Nevertheless, the authors critically conclude that the confidence intervals were wide and that a clinically important effect cannot be excluded [143].

Other aspects of LTG need to be considered, especially in women of childbearing age, as it is known that plasma levels of LTG may drop to less than 50% in concomitant use of oral contraceptives [144–146], largely due to increased glucuronidation [147], leading to higher seizure frequencies [144]. Similarly, the oral clearance of LTG, but also of levetiracetam and other AEDs, is strongly enhanced during pregnancy which can also be associated with an increased seizure frequency [148]. This may put pregnant women with epilepsy and GTCS or FBTCS at an elevated risk. In this context, a UK series including 11 SUDEP cases during or shortly after pregnancy found that 9 women were on LTG (7 on monotherapy) [149]. This finding may only reflect prescribing practice, but may also underscore that specific features of AED should be considered when counselling women with epilepsy.

6.2.2 Pharmacological control of FBTCS in focal epilepsies

As for GTCS and generalized genetic epilepsies, efficacy data of specific AEDs or head-to-head comparisons between different AEDs for focal epilepsies and FBTCS are scarce. A meta-analysis of randomized placebo-controlled trials has examined the responder rate of patients with FBTCS upon seven AEDs (lacosamide, perampanel, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide). Only lacosamide, perampanel and topiramate were significantly more efficacious than placebo, and pregabalin was less efficacious than the 3 AEDs [150]. AEDs that were apparently not more efficacious than placebo (tiagabine, vigabatrin, zonisamide) had the smallest sample sizes, possibly explaining the lack of superiority as compared to placebo. A more recent pooled analysis of several phase 3 studies yielded that brivaracetam was also more efficacious in controlling FBTCS as compared to placebo [151].

In conclusion, AED efficacy and safety can depend on the epilepsy syndrome in which it is used, and effective treatment of GTCS and FBTCS is crucial to reduce the incidence of SUDEP. The question of whether LTG is harmful in specific constellations has not satisfactorily been answered yet, but available evidence suggests that the use of LTG may increase the risk of SUDEP in female epilepsy patients with generalized genetic epilepsy.

6.3 Non-pharmacological seizure control

In two thirds of people with epilepsy, long-term seizure freedom can be achieved by regular AED intake. In the remaining third, non-drug-based procedures offered at specialized epilepsy centers, such as resective epilepsy surgery and neurostimulation devices (vagal nerve

stimulation, stimulation of the anterior thalamic nucleus, brain responsive stimulation) were all shown to reduce the seizure frequency and SUDEP rate [152–155].

6.4 Transfer of knowledge

Informing and educating the patients and their relatives and caregivers on the risk of SUDEP and on the role of treatment adherence in risk reduction has already been included in the guidelines of major neurological associations, such as the American Academy of Neurology (AAN) [3]. Currently, up to almost 90% of patients with epilepsy who have been interviewed at a major epilepsy center have never heard of SUDEP [156]. According to this poll, about 50% were interested to learn more about SUDEP. A survey among German-speaking physicians who are involved in the treatment of people with epilepsy revealed that about two-thirds of respondents rarely or never educate their patients on SUDEP [157]. A common argument against informing patients with epilepsy and their relatives about SUDEP is the motivation to avoid additional tension and anxiety. The education and information about SUDEP, however, seem to have no negative impact on the mood or quality of life of parents of children with epilepsy or adults with chronic epilepsy, as prospective studies have shown [158–160]. To reduce the risk of negative reactions to information about SUDEP, it is also recommended to emphasize that only one out of every 1000 adults and one in about 4500 pediatric epilepsy patients per year die from SUDEP, while 999 out of 1000 adults and 4499 out of 4500 children do not [3]. Positive effects of patient education may be a better drug adherence, as recently suggested by a prospective clinical study [161].

6.5 Simple measures and nightly supervision

Even with optimal treatment adherence, a substantial number of patients remain refractory to therapy and are at high risk of SUDEP. In the best case, the above-described fatal SUDEP cascade may be interrupted early by simple measures such as positioning of the patient into the stable, lateral recovery position, or by nasal administration of oxygen. Cardiopulmonary resuscitation starting early after seizure cessation may also prevent SUDEP, as suggested by observations of the MORTEMUS study [24]. One obvious reason for the high SUDEP rate during night is that caregivers are mostly sleeping and that seizures are unnoticed. Even during inpatient video-EEG monitoring, supervision by professional personnel is more effective during the day [24]. Two case-control studies, one with 153 SUDEP cases and 612 controls [118] and the other with 60 SUDEP cases and 198 controls in two different care settings [162], examined the effects of night-time supervision. The former showed a significant reduction in SUDEP rates through the presence of a roommate or home audiometric monitoring and the latter found a threefold lower SUDEP incidence rate in the nursing home with higher levels of nocturnal supervision (e.g. roommates, audio surveillance, video surveillance, bedside motion detectors, walking tours every 15 minutes). In conclusion, nightly supervision and responsive support systems are promising tools, although the quality of evidence was still considered low in a systematic review of 2016 [163]. Furthermore, as an easy-to-implement mechanical prevention measure, lattice anti-asphyxia pillows are recommended to improve postictal respiratory mechanics [164].

6.6 Device-Based Seizure Detection

Probably about 90% of the SUDEP cases are related to TCS [81], suggesting that accurate and real-time detection of TCS may help to alleviate the risk of SUDEP. In recent years, numerous

20

monitoring devices have been developed that are able to detect TCS with increasing sensitivity and specificity by analyzing biosignals [165]. The technologies for such devices include quasi-piezoelectric mattresses [166] and portable sensors using accelerometry [167], electrodermal resistance [168], pulse acceleration and electromyography [169] or ECG activity [170]. Given an acceptable performance (i.e. high sensitivity, low false positive alarms), the monitoring devices could send alarms to caretakers, allowing simple measures to be taken [34] or timely onset of cardiopulmonary resuscitation (CPR) that may prevent SUDP [24]. It is, however, unclear whether the TCS-triggered cascade of apnea and bradyarrhythmia is reversible by CPR in every case [171]. Automatic seizure detection over long periods of time is nevertheless very helpful, as it reveals commonly unobserved nocturnal seizures, which should prompt adaptation of the individual therapy regimes and ultimately reduce the risk of future TCS and possibly SUDEP.

7. Expert Opinion

Targeted SUDEP prevention is still an unmet need and prospective controlled clinical trials to test effects on SUDEP rate are difficult for various reasons (e.g. due to relatively low frequency with a high number of study participants required, ethical concerns). There is, however, very strong evidence that TCS are the major and modifiable risk factor and that most SUDEP cases are directly related to TCS. Therefore, it is reasonable to assume that every measure which helps to control TCS would ultimately lead to a meaningful reduction of SUDEP risk and rate. The question of whether specific AEDs are linked to SUDEP is still controversially discussed, as AEDs vary in their efficacies to control TCS and their cardiovascular profile. This issue needs further efforts to be elucidated. Controlled clinical trials with anti-seizure treatments (AEDs, neuromodulatory devices) to improve control of TCS would be a straightforward and most

pragmatic way to advance clinical practice. Furthermore, the use of approved wearable devices for automatic seizure detection would greatly help to accurately count the number of TCS and to enhance the quality of such clinical trials. Inventories and safety checklists developed to assess the individual risk of people with epilepsy may help to further identify patients at highest risk and candidates for such trials [172–175]. In contrast, the identification of single genetic or imaging biomarkers of a high SUDEP risk appears rather unlikely to us for several reasons: People can suffer from many TCS before the fatal SUDEP cascade is triggered, but there are also cases in which SUDEP occurs with the first TCSs, i.e. the fatal cascade can be triggered in principle in every patient, but requires several "random" factors to occur simultaneously (the 'perfect' storm); SUDEP is likely to be a heterogeneous entity (TCS-related, non-TCS related, not seizure-related at all) and even in the predominant TCS-related SUDEP cases, the diversity of individual and epilepsy-related features makes the identification of meaningful biomarkers quite unlikely; life-style factors and treatment adherence are rather difficult to assess in a proportion of SUDEP cases, but may also contribute to occurrence of SUDEP. The modulation of putative downstream mechanism, e.g. postictal apnea due to deficits in serotoninergic signaling, requires prospective clinical trials in a video-EEG controlled environment. This would be a further treatment option for those in whom full control of TCS cannot be achieved. The role of the prone position as a facilitating factor for SUDEP requires further attention and methods to protect people from turning into the prone position during the course of a TCS may be a simple measure to reduce the SUDEP risk.

While some epidemiological risk factors are already well established, over the next five years, genetic and molecular research will be continued with the goal to delineate specific

vulnerabilities to SUDEP of individual patients and patient groups [176]. Furthermore, new molecules might extend pharmacological treatment options, and advanced techniques in seizure onset localization might increase the proportion of patients eligible for resective epilepsy surgery. Machine learning methods are already an integral part of epilepsy applications [177]. Here, despite methodological challenges [178], future algorithms might be able to not just detect, but also to predict epileptic seizures in a manner that has an impact on the daily life of people with chronic epilepsy [179]. Implementing these techniques into therapeutic devices [180,181] would fundamentally change the abilities of epilepsy diagnostics, and might even revolutionize the prevention of seizures and SUDEP. Finally yet importantly, enhanced education of people with epilepsy and their relatives, as well as of health care professionals, will be crucial to raise awareness and strengthen efforts to prevent SUDEP.

8. Article Highlights

- SUDEP is a rare but fatal complication of epilepsy

- The majority of SUDEP cases are linked to epileptic seizures, a minor portion occurs in the absence of signs of epileptic seizures

- SUDEP mostly occurs in association with nocturnal and generalized or focal to bilateral tonic-clonic seizures

- The lethal, probably reversible cascade includes postictal central apnea followed by bradyarrhythmia and asystole

- Effective seizure control and nocturnal supervision are key elements to prevent SUDEP in most cases

- Automatic seizure detection devices are likely to reduce the SUDEP risk

23

- Machine learning algorithms and novel wearable technologies may improve seizure prediction and detection, significantly boosting SUDEP prevention

- Education of patients, relatives and health care professionals about SUDEP is highly recommended

24

9. Reference annotations:

Nashef L, Epilepsia, 2012 *: Consensus on SUDEP definition and related terminology.

Nilsson L, Lancet, 1999 *: Early case-control study describing SUDEP as a seizure related event.

Langan et al., JNNP 2000 *: Series of witnessed SUDEP cases revealing that TCS are likely to play a major role

Ryvlin P, Lancet Neurology, 2013 **: Collection of monitored SUDEP cases worldwide to disentangle the time course of events leading to SUDEP.

Ryvlin et al., Lancet Neurology, 2011 **: Meta-analysis of randomized placebo-controlled trials showing that effective antiepileptic drug treatment is associated with lower SUDEP rates

Harden C, Neurology, 2017 *: Practical guidelines for the clinician dealing with epilepsy patients regarding SUDEP risk factors and preventive measures, stressing TCS as primal risk factor.

Radhakrishnan DM, Acta Neurol Scand, 2018 *: Showing a trend towards an improved drug adherence after education on SUDEP.

DeGiorgio CM, Acta Neurol Scand, 2019 *: Ranking of risk factors for SUDEP by comparing relative risk ratios.

10. Declaration of interests:

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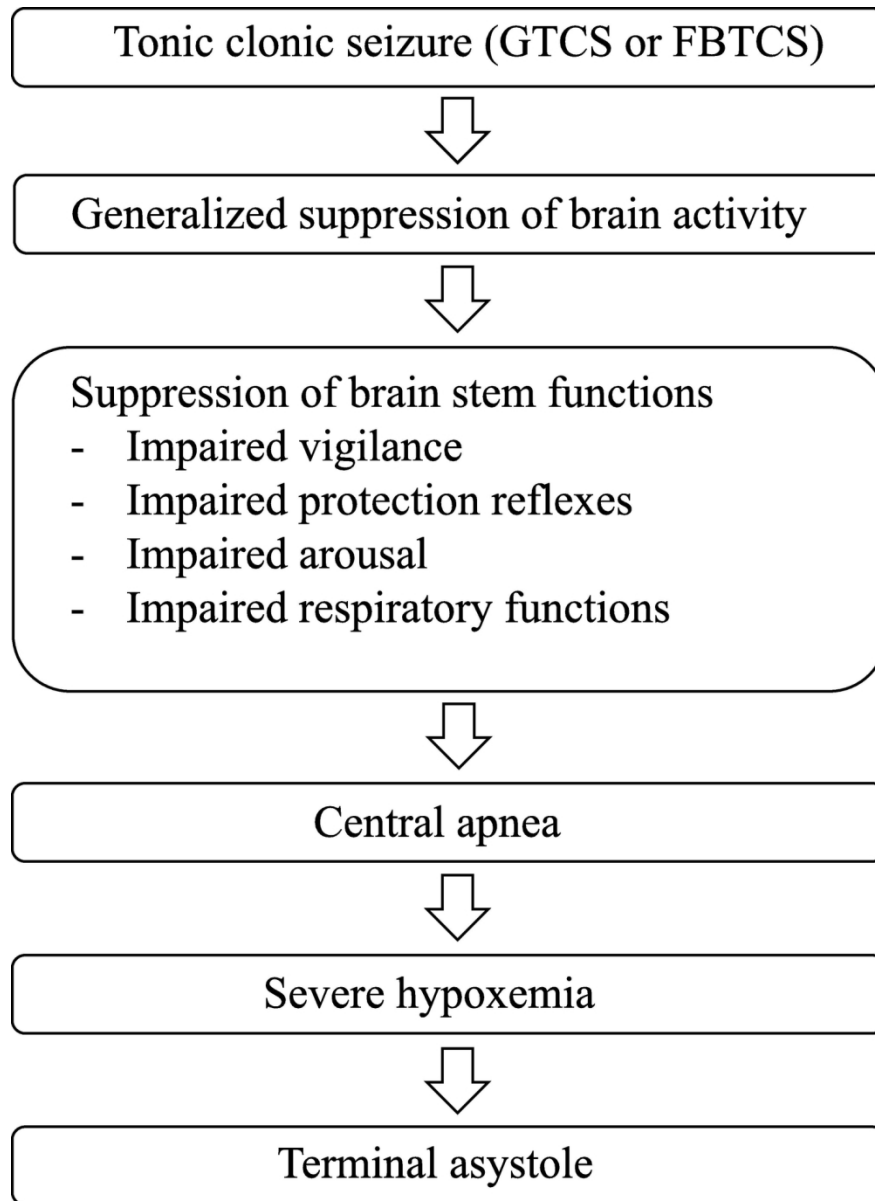
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Figure 1: The neurovegetative breakdown in SUDEP

124x170mm (300 x 300 DPI)

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Table 1. Definitions of SUDEP (according to Nashef L, Epilepsia, 2012 [1]).

1. Definite SUDEP*	Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration ≥30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death
1a. Definite SUDEP Plus*	Satisfying the definition of Definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death
2. Probable SUDEP / Probable SUDEP Plus*	Same as Definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death
3. Possible SUDEP*	A competing cause of death is present
4. Near-SUDEP / Plus	A patient with epilepsy survives resuscitation for more than 1h after a cardiorespiratory arrest that has no structural cause identified after investigation
5. Not SUDEP	A clear cause of death is known
6. Unclassified	Incomplete information available; not possible to classify

*If a death is witnessed, an arbitrary cutoff of death within 1 hour from acute collapse is suggested.