




Reducing Sudden Unexpected Death in Epilepsy: Considering Risk Factors, Pathophysiology and Strategies

Nathan A. Shlobin, BA¹
Josemir W. Sander, MD, PhD, FRCP^{2,3, *} 

Address

¹Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

²UCL Queen Square Institute of Neurology, NIHR University College London Hospitals Biomedical Research Centre, London WC1N 3BG, Chalfont Centre for Epilepsy, WC1N 3BG Chalfont St Peter, UK

Email: l.sander@ucl.ac.uk

³Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, the Netherlands

Published online: 3 November 2021

© The Author(s) 2021

This article is part of Topical Collection on **Epilepsy**

Keywords Premature mortality · Seizure · SUDEP

Abstract

Purpose of Review Sudden Unexpected Death in Epilepsy (SUDEP) is the commonest cause of epilepsy-related premature mortality in people with chronic epilepsy. It is the most devastating epilepsy outcome. We describe and discuss risk factors and possible pathophysiological mechanisms to elucidate possible preventative strategies to avert SUDEP.

Recent Findings Sudden death accounts for a significant proportion of premature mortality in people with epilepsy compared to the general population. Unmodifiable risk factors include a history of neurologic insult, younger age of seizure-onset, longer epilepsy duration, a history of convulsions, symptomatic epilepsy, intellectual disability, and non-ambulatory status. Modifiable risk factors include the presence of convulsive seizures, increased seizure frequency, timely and appropriate use of antiseizure medications,

polytherapy, alcoholism, and supervision while sleeping. Pathophysiology is unclear, but several possible mechanisms such as direct alteration of cardiorespiratory function, pulmonary impairment, electrocerebral shutdown, adenosine dysfunction, and genetic susceptibility suggested.

Summary Methods to prevent SUDEP include increasing awareness of SUDEP, augmenting knowledge of unmodifiable risk factors, obtaining full seizure remission, addressing lifestyle factors such as supervision and prone positioning, and enacting protocols to increase the detection of and intervention for SUDEP. Further studies are required to characterize precisely and comprehensively SUDEP risk factors and pathophysiological drivers and develop evidence-based algorithms to minimize SUDEP in people with epilepsy.

Introduction

Epilepsy is a common neurologic condition estimated to affect up to 70 million people globally. Its incidence ranges from 45 per 100,000 individuals annually in high-income countries to about 82/100,000/year in low and middle-income countries. [1–3].

People with epilepsy are at increased risk for premature mortality compared to the general population [4–11]. Epilepsy ranks as the fifth-highest cause of years life lost before age 75 for males and eighth highest for females [12], while symptomatic epilepsy may reduce life expectancy by up to 18 years [13]. Causes of death in epilepsy may be stratified as those attributable to epilepsy, resulting from the underlying pathology, and unrelated [14]. Pneumonia,

central nervous system (CNS) and non-CNS neoplasms, and cerebrovascular disease are common causes of death [6, 15]. Deaths resulting from accidents, status epilepticus, accidents, and sudden unexpected death in epilepsy (SUDEP) are considered epilepsy-related [16].

SUDEP epitomizes the commonest epilepsy-related cause of premature death [17], and it is the most upsetting outcome of epilepsy. Little is known about strategies to reduce SUDEP risk. This review aims to characterize SUDEP, describe pathophysiology and risk factors, and delineate preventative strategy to reduce it. We also discuss gaps in existing knowledge and indicate areas for future research.

Definition of SUDEP

The definition of SUDEP is death in a seemingly healthy individual with epilepsy not resulting from accident, trauma, status epilepticus, or other identifiable causes [18–21]. A definitive SUDEP diagnosis is when clinical criteria are met, and no other cause of death is identified on a full anatomical and toxicological post-mortem examination, through evidence of seizures may be present [22]. SUDEP is probable when clinical criteria are met, but an autopsy is lacking and possible when there is an alternative cause of death or a lack of clinical data [23]. SUDEP definition is widely accepted, but it has shortcomings. The definition encompasses heterogeneous cases, preventing differentiation of pathophysiology of SUDEP cases occurring in seizures from that of SUDEP cases that occur without evidence for seizures [21]. The definition excludes potentially life-threatening simultaneous pathological processes, preventing the determination of increased risk associated with epilepsy in

the presence of concomitant disease [20]. The classification of many cases as “possible SUDEP” in clinical practice is due to a scarcity of information or other plausible explanations for death.

Epidemiology of SUDEP

The sudden death rate in young people with epilepsy is nearly 24 times higher than the general population [24]. The risk of SUDEP varies by population, criteria, SUDEP definition and study methods [20, 25]. Table 1 shows the incidence of SUDEP for different populations [8, 9, 24, 26–53]. Unselected cohorts report the lowest incidence rates, at 0.09 to 0.35 per 1000 person-years [8, 24]. More commonly, the incidence of SUDEP is estimated and based on the assumed prevalence of epilepsy in the region after SUDEP cases are identified after a review of post-mortem records [20]. Most frequently, SUDEP cases are identified from among cohorts of people with epilepsy from medical records or databases [20]. SUDEP is the leading cause of premature death among children and adults, comprising 10–50% of all deaths in people with chronic epilepsy seen at tertiary care centers [9, 39–42, 44]. A cohort study determined children had a 7% cumulative risk of dying suddenly within 40 years, accounting for 38% of all deaths, nearly all in adulthood [11]. SUDEP is less common in children than in adults. In children SUDEP, occurs mostly in those with major neurologic impairment or genetics syndromes such as Dravet’s [11, 54–56]. Additionally, epilepsy occurs in 6.6% of individuals with sudden arrhythmic death syndrome [57]. Given similarities of SUDEP and sudden arrhythmic death syndrome, the true SUDEP incidence may be larger than previously described [58].

Table 1: Incidence of SUDEP by Population

Population	Incidence (per 1000 person-years)
Unselected cohorts of epilepsy cases	0.09 - 0.35
People with epilepsy	0.9 - 2.3
Chronic refractory epilepsy	1.1 - 5.9
Candidates for epilepsy surgery	6.3 - 9.3
Vagus nerve stimulation	1.7 - 2.5
Responsive neurostimulation	2.0
Epilepsy in remission	0.4

SUDEP Risk Factors

Studies have sought to identify SUDEP risk factors. Early uncontrolled studies identified male sex, young age, poor adherence with antiseizure medication (ASM) treatment, and alcohol overuse [17]. These studies are difficult to interpret given selection bias and the absence of controls [20]. Newer studies have employed control groups. These studies have yielded different results and risk factors through variation in SUDEP definition, population, risk factors examined, methodology, and study design [20, 59]. Nonetheless, identifying risk factors is vital to improving risk stratification and SUDEP prevention.

Unmodifiable Risk Factors

Unmodifiable SUDEP risk factors have been scrutinized. Male sex is associated with a greater risk [29, 31, 60, 61]. The mechanism is unclear, and other studies have shown either a similar SUDEP incidence in males and females or increased incidence in females [31, 33, 40, 62]. History of a significant neurologic insult is also associated with an increased SUDEP risk [11, 54, 55]. Younger age of onset has also been associated with SUDEP [24, 25, 31, 59, 60, 63], indicating an earlier developmental age may provide a substrate for deleterious effects of seizures. Longer duration of epilepsy is a risk [17, 19, 25, 32, 59, 62, 63], perhaps due to cumulative neurological injury resulting from repeated seizures. People with a history of convulsions are also more likely to succumb to SUDEP [25, 31]. Others, however, have reported no association between SUDEP and history of convulsions [63, 64]. Symptomatic epilepsy is also associated with SUDEP [19, 59, 60]. This may serve as a proxy for severity [19], as symptomatic seizures may promote more significant neurologic damage. Associated intellectual disability appears to predispose individuals to SUDEP [28, 32, 43, 59, 65], although often studies have lacked a clear definition of the nature and degree of intellectual disability [65]. Non-ambulatory status is also associated with SUDEP [28], potentially explained by a concomitant insult in the CNS. Knowledge of unmodifiable risk factors is essential for clinicians when counseling people with epilepsy and caregivers.

Modifiable Risk Factors

Some modifiable risk factors are directly related to the character of epilepsy. The presence of convulsive seizures may be the most critical SUDEP risk factor [59, 62] associated with a 27-fold increase in risk, while individuals with other seizure types do not have such an increase [66]. Similarly, the presence of nocturnal convulsions is associated with a 15-fold risk increase [66, 67]. A greater frequency of seizures, particularly convulsive seizures, is likely associated with SUDEP via seizure-induced pathophysiological changes [17, 25, 31, 32, 59, 62, 64, 68, 69]. Seizure frequency may increase in the months

preceding SUDEP by one-quarter [62, 70], perhaps reflecting progressively more inadequate seizure control anticipating a fatal outcome [31, 32, 43, 54].

Treatment-related factors have also been implicated. Increased time since the last ASM prescription is associated with a greater SUDEP risk. [62] Poor adherence may increase SUDEP risk by 50%, particularly if seizures persist [17, 62, 71, 72]. Treatment that is not evidence-based is also associated with SUDEP due to failure to decrease or stop seizures [62]. Sudden and frequent ASM dosage changes are associated with greater SUDEP risk, [31] likely reflecting poor seizure control or increased severity. ASM polytherapy has also been associated with a greater likelihood of SUDEP [15, 17, 25, 31, 32, 59]. Polytherapy may be a surrogate for seizure frequency [73], and studies have indicated that increased SUDEP risk with polytherapy persists when controlling for seizure frequency, suggesting greater risk cannot be explained by increased seizure frequency alone [31]. A recent study determined that polytherapy is associated with reduced SUDEP risk, particularly in combinations including lamotrigine, valproic acid, and levetiracetam [72].

Studies have provided conflicting evidence regarding the role of specific ASMs. One reported SUDEP incidence was greater in Norwegian women treated with lamotrigine, perhaps resulting from seizure type, coupled with a genetic predisposition [74]. In another study, lamotrigine therapy was associated with significantly greater SUDEP risk in individuals with generalized epilepsy [59]. No increase in SUDEP risk was found when controlling for the frequency of convulsions [59]. Still, the United States Food and Drug Administration has recently placed a warning on lamotrigine for individuals with possible cardiac co-morbidity [75]. Other studies have found carbamazepine therapy or high levels of carbamazepine in people on polytherapy or frequent dose changes increased the risk of SUDEP [64, 76, 77]. Another study determined that users of levetiracetam had the lowest risk of SUDEP in monotherapy [72]. Others have not found a difference in SUDEP risk based on the used ASM [32, 78]. There may be no difference in risk associated with monotherapy, polytherapy, or particular ASMs when controlling for the number of generalized tonic-clonic seizures [79]. Instead, failure to control for confounding variables may explain the apparent differences [25, 80].

Additionally, we must also discuss modifiable risk factors unrelated to epilepsy. SUDEP is associated with substance use disorders and alcohol dependence [27, 29, 59, 61, 62, 66]. A case-control study, however, failed to reinforce this association [31], while few studies examine this factor. Further studies are required to investigate potential mechanisms. Statin use is reported to be associated with reduced SUDEP risk [72], either due to physiological effects or as a proxy of improved compliance. Additionally, living alone is related to a fivefold increased SUDEP risk [66]. Similarly, a combination of not sharing a bedroom and convulsions associates with a 67-fold higher SUDEP risk [66]. The presence of supervision by sharing the same bedroom or employing precautions such as a listening device may be protective against SUDEP by allowing cohabitants to identify changes in seizure frequency or quality and seek medical care before SUDEP [64].

Pathophysiology of SUDEP

SUDEP mechanisms remain mostly undefined, but recent studies have yielded proposed mechanisms by which nonmodifiable and modifiable factors may increase SUDEP risk. The pathophysiology of SUDEP is likely multifactorial, consisting of seizure-induced cardiorespiratory changes, intrinsic pulmonary and cardiac dysfunction, individual positioning, loss of arousal, sleep, and genetic mutations [68]. The mechanisms of death in SUDEP may overlap considerably with sudden arrhythmic death syndrome [57, 58].

Direct Seizure-Induced Alteration in Cardiorespiratory Function

The MORTEMUS study examined 16 SUDEP cases and nine near SUDEP cases in EEG monitoring units [81]. The study determined that a convulsion prompted early postictal neurologically-mediated alteration in cardiorespiratory function, leading to immediate death or a period of restored cardiorespiratory function preceding cardiac arrest secondary to terminal apnea [81]. Though rare, non-seizure related SUDEP indicates the seizures are not necessary to trigger fatal cardiorespiratory dysfunction [82]. Autonomic dysfunction may predispose people with epilepsy to SUDEP due to alterations in cardiorespiratory function in seizure and non-seizure cases [83, 84].

Additional studies examining respiratory monitoring techniques have indicated that ictal respiratory dysfunction is common and may be severe [68]. Greater than half of the people undergoing long-term video EEG monitoring had apnea during seizures, of whom almost two-thirds had decreases in oxygen saturation below 85% [85]. Another determined oxygen saturation decreased below 90% in a third of seizures [86]. Measurements of nasal airflow and respiratory effort indicate that central apnea or hypopnea occurs in half of the seizures, and mixed or obstructive apneas occur in one-tenth of seizures [86]. Seizures were also associated with severe prolonged increased ET_{CO₂} levels, greater than 50 mmHg in a third of people [86, 87]. Clearly, respiratory disturbances resulting from seizures may result in SUDEP.

Similarly, seizures impinge on cardiac function [68]. One study showed that almost all seizures increase heart rate, including sinus tachycardia in all convulsions and in three-quarters of focal seizures [88]. Another noted tachycardia in 87% of seizures, significantly more in mesial temporal epilepsy than other temporal or extratemporal epilepsy [89]. About a fifth of seizures and over a third of cases have associated ECG abnormalities other than sinus tachycardia, most of which are benign [90]. In contrast, seizure-induced bradycardia occurs in approximately 1.4% of all seizures [89], while ictal asystole occurs in 0.27% to 0.4% of cases [91, 92]. In addition to changes in heart rate, arrhythmias and asystole occur after seizures. A study reported only 6% of seizures, experienced by 10% of cases, were associated with malignant ECG abnormalities such as ST-segment depression and T-wave inversion [88]. Another study detected the ictal prolongation of the QT_c interval in 16% of seizures [90]. QT_c prolongation may increase the likelihood of polymorphic

ventricular tachycardia and sudden cardiac death [93]. Additionally, alterations in heart rate variability in epilepsy may contribute [68]. People with temporal epilepsy have reduced heart rate variability, particularly at night [94]. Precise mechanisms have yet to be elucidated. One proposed mechanism is the activation of pathways that project to neurons in the brainstem controlling autonomic output to the cardiovascular system by seizures [95]. At the same time, another posits seizure-induced apnea and oxygen desaturation lead to autonomic responses that reduce heart rate variability [96]. Reduced heart rate variability is associated with more significant cardiac mortality and sudden cardiac death [97]. Cardiac alterations resulting from seizures may lead to SUDEP.

It is unknown whether changes in heart rate, arrhythmias, and asystole are secondary to seizure-induced respiratory changes, given the lack of measurement of respiratory parameters in these studies [68]. Hypoxemia, hypoventilation, and apnea may promote secondary autonomic changes that affect cardiac function [68]. Seizure-induced QT changes are associated with concomitant hypoventilation and oxygen desaturation [98], indicating respiratory dysfunction may lead to abnormalities in cardiac tissue repolarization. Hypoxemia leads to bradycardia in people with apnea [99, 100]. Another reported peri-ictal bradycardia preceding asystole in an individual with concurrent oxygen saturation less than 50%, indicating bradycardia and asystole may have resulted from hypoventilation-induced hypoxemia [86]. Peri-ictal hypoxemia is associated with contralateral spread on EEG and postictal generalized EEG suppression [101, 102], reflecting the spread of seizures to brainstem respiratory centers [96]. Cardiac susceptibility to peri-ictal respiratory dysfunction may mediate the risk of SUDEP [68].

Pulmonary Impairment

SUDEP's likely pulmonary pathophysiology consists of an interplay between intrinsic pulmonary dysfunction, positioning, and alterations in breathing during sleep. Intrinsic pulmonary dysfunction occurs, demonstrated by hypercapnia and oxygen desaturation, during the postictal period, when respiratory effort may be preserved or increased [87, 101]. Seizure-induced changes in pulmonary blood flow or may result in a mismatch between ventilation and perfusion [68]. This evidence is, however, circumstantial given direct measurements of respiratory function [68]. Pulmonary edema is another possible manifestation of intrinsic pulmonary dysfunction resulting in SUDEP; however, the edema is usually mild and thought to be unable to cause death alone [81].

Ictal respiratory dysfunction may only be fatal under the appropriate conditions [68]. People who die of SUDEP are often found lying in the prone position. The mouth and nose may be occluded, increasing the risk of asphyxia in people with decreased arousal secondary to hypoventilation-induced hypercapnia [68, 81]. The prone position is infrequent among closely observed nonfatal convulsive seizures [103]. In the MORTEMUS study, there was no attempt to optimize the positioning of cases from the prone position

between seizure termination and death, perhaps promoting hypoxia [81]. Suppression of brainstem arousal centers and potential loss of consciousness may result from decreased activity of serotonergic neurons in the midbrain. In contrast, impaired breathing and repositioning of the mouth and nose may result from the postictal reduction in serotonergic neurons in the medulla [104–106].

Similarly, that most SUDEP occurs at night indicates circadian processes influencing breathing and arousal may be involved [81, 107]. Breathing is unstable at sleep onset due to cessation of respiratory stimuli involved in arousal [108], often leading to hypoventilation or apnea [68]. Additionally, sleep is associated with reduced ventilatory response to hypercapnia, hypercapnia, and ventilatory loading [109–111]. Sleep-disordered breathing is more likely to occur in people with high SUDEP risk [112]. Similarly, sleep apnea may be more common in people with epilepsy, mainly when seizures are poorly controlled [113–115]. In contrast, obstructive apnea may occur in susceptible individuals due to decreased upper airway dilator tone [116]. People with epilepsy who die during sleep are more likely to be in the prone position than those who die during wakefulness, while nocturnal seizures were associated with a 6.3 times greater likelihood of dying in the prone position than diurnal seizures [117]. Prone positioning and sleep may interact to increase risk synergistically.

Electrocerebral Shutdown

Another proposed mechanism is electrocerebral shutdown. The MORTEMUS study reported prolonged postictal generalized EEG suppression promoting electrocerebral shutdown might mediate cardiorespiratory dysfunction in SUDEP [81]. Other studies have provided inconsistent evidence regarding the role of this mechanism [118, 119]. Postictal generalized EEG suppression occurred more frequently at night, perhaps promoting central apnea and asystole [81]. Other studies have not confirmed this finding [120, 121].

Adenosine Dysfunction

Disruption of adenosine has also been implicated in SUDEP [68, 122]. Adenosine is involved in the brainstem-mediated cardiorespiratory function and anticonvulsive action via modulation of synaptic transmission and neuronal activity [120–123]. This suggests that adenosine dysfunction may reduce seizure thresholds and increase the probability of cardiorespiratory function secondary and unrelated to seizures. High-risk individuals have decreased distribution of adenosine A_{2A} receptors in the temporal lobe, indicative of glial dysfunction [122]. Greater neuronal A_{1A} receptor distribution in high-risk cases may promote peri-ictal amygdala dysfunction in SUDEP [122]. Adenosine receptor antagonists, including caffeine, may protect against SUDEP if administered at the beginning of the seizure [124].

Genetic Susceptibility

Some people who die from SUDEP may have a genetic susceptibility. Table 2 delineates genes implicated in SUDEP. People with Dravet Syndrome, most often associated with mutations in the SCN1A gene, experience greater rates of SUDEP than the general epilepsy population, with half of all deaths attributable to SUDEP [56, 125]. This may result from postictal hypoventilation and bradycardia due to increased cardiac conduction disease susceptibility [126, 127]. People with KCNT1 mutations have mortality from SUDEP akin to Dravet syndrome, possibly resulting from pulmonary and cardiovascular abnormalities [128]. There is conflicting evidence regarding whether people with mutations in the SCN8A may have an increased SUDEP risk [129]. Mutations may directly affect the cardiorespiratory function or providing an additional risk factor for SUDEP [129]. Isodicentric chromosome 15 syndrome is also associated with SUDEP through the high frequency of associated refractory epilepsy, intellectual disability, and non-ambulatory status [130]. Mutations in genes associated with epilepsy such as SCN2A, DEPDC5, KCNA1, HCN2, and PRRT2 and genes associated with either long-QT syndrome such as KCNQ1, KCNH2, and SCN5A or other cardiac arrhythmias such as RYR2 have been implicated in SUDEP [127, 131]. Future studies are necessary to precisely characterize the scope of pathophysiological mechanisms of SUDEP.

Prevention of SUDEP

SUDEP's prevention requires delineation of its epidemiology in specific populations, accurate SUDEP classification, and further investigation of risk factors and pathophysiological mechanisms. Clinicians, coroners, epidemiologists, health officials, researchers, administrators, and people with epilepsy and caregivers must be involved in the initiatives to prevent SUDEP. Broad themes include raising awareness, addressing risk factors, and implementing hospital protocols. Specific algorithms may be instrumental in preempting SUDEP.

Building Awareness of SUDEP

Increasing awareness among the medical community, people with epilepsy, and caregivers are essential to address SUDEP. Increased knowledge of SUDEP will ensure that cases of potential SUDEP are referred to a coroner for determination [73]. Accurate reporting and classification of SUDEP may enable investigators to identify risk factors and prevention strategies [73]. Many adults with epilepsy and people who lost a loved one from SUDEP are unaware of SUDEP [132, 133]. There is a discrepancy between physicians' provided information and what individuals seek. The majority of clinicians do not routinely discuss SUDEP and are uncertain about the effect of this information on people with epilepsy or caregivers [134–136]. In contrast, most

Table 2: Genes Implicated in SUDEP

Gene	Function	Condition
SCN1A	Voltage-gated Na ⁺ channel	Dravet syndrome
KCNT1	Na ⁺ -activated K ⁺ channel	Migrating partial seizures of infancy Autosomal dominant nocturnal frontal lobe epilepsy
SCN8A	Voltage-gated Na ⁺ channel	Early infantile epileptic encephalopathy Benign familial infantile seizures-5 and paroxysmal dyskinesia
NA	Isodicentric chromosome 15	Dup15q syndrome
SCN2A	Voltage-gated Na ⁺ channel	Benign familial neonatal / infantile seizures Infantile spasms Severe early-onset epileptic encephalopathies Intellectual disability
DPEDC5	Production of part of the GATOR1 complex to regulate mTOR	Familial focal epilepsy with variable foci Autosomal dominant nocturnal frontal lobe epilepsy
KCNA1	Delayed rectifier voltage-gated K ⁺ channel	Autosomal dominant epilepsy with auditory features Familial mesial temporal lobe epilepsy Infantile spasms
HCN2	Hyperpolarization-activated nucleotide-gated ion channel	Episodic ataxia type 1
PRRT2	Transmembrane protein	Epilepsy
KCNQ1	Delayed rectifier voltage-gated K ⁺ channel	Epilepsy
KCNH2	Delayed rectifier voltage-gated K ⁺ channel	Benign familial infantile seizures
SCN5A	Voltage-gated Na ⁺ channel	Paroxysmal kinesigenic dyskinesia with infantile convulsions Long QT syndrome type 1 Long QT syndrome type 2 Long QT syndrome type 3
RYR2	Ca ²⁺ channel	Sudden infant death syndrome Long QT syndrome, arrhythmias

people with epilepsy and caregivers want to receive information regarding SUDEP [132, 133, 137, 138]. Low information provision by clinicians may result from the perception of adverse reactions from individuals and caregivers [134]. Having epilepsy or neurophysiology training is associated with an increased likelihood of perceived negative response, but years in practice and seeing adults and children are associated with decreased negative response likelihood [134]. People with epilepsy feel it is their right to be informed regardless of increased fear [138]. Training and practice-related factors affect the provision of SUDEP information. The number of people with epilepsy seen annually and having seen a person who had SUDEP within the preceding two years independently predict discussing SUDEP nearly all of the time [134]. Besides increasing awareness, providing information about SUDEP to people with epilepsy and caregivers improve medication adherence and management of lifestyle factors that lower seizure threshold without decreasing mood or quality of life [138, 139].

Knowledge of Unmodifiable Risk Factors

Unmodifiable risk factors cannot, by definition, be altered. Awareness of the role history of neurologic insult, younger age of epilepsy onset, longer duration of epilepsy, a history of generalized tonic-clonic seizure during the night, symptomatic epilepsy, intellectual disability, and non-ambulatory status may provide numerous advantages in reducing the risk of SUDEP [11, 17, 19, 24, 25, 28, 29, 31, 32, 43, 54, 55, 59–63, 65]. This knowledge will allow clinicians to counsel people with epilepsy and caregivers. In turn, increased awareness among cohabitants and caregivers may promote greater vigilance and a lower threshold for seeking medical care. Additionally, knowledge of these factors will allow clinicians to enact specific imaging and treatment algorithms. Lastly, this will promote communication and coordination among care providers.

Reducing or Stopping Seizures

Reducing the frequency of convulsions is central to efforts to prevent SUDEP [59, 62]. Comprehensive education may help improve adherence to ASMs. Managing lifestyle factors that may contribute to SUDEP, increasing knowledge regarding treatment medication interactions, improve reaction to seizures, and increasing self-efficacy [138–140]. Similarly, utilization of evidence-based ASMs treatment strategies, avoidance of sudden and frequent changes in ASM dosing, and minimization of polypharmacy to the extent possible may also reduce SUDEP [15, 17, 25, 31, 32, 59, 62]. Using levetiracetam in suitable cases may be optimal [72]. If polypharmacy is necessary, ASM combinations including lamotrigine, valproic acid, and levetiracetam should be considered [72]. Epilepsy surgery, vagus nerve stimulation, or responsive

neurostimulation in well-selected patients may reduce seizure frequency in patients refractory to ASM [42, 48–51].

Lifestyle

Addressing lifestyle factors will reduce the risk of SUDEP. Management of co-morbidities, such as hyperlipidemia, may prevent SUDEP [72]. Similarly, addiction care for individuals with epilepsy who with substance use disorders or alcohol dependence may reduce the risk of SUDEP [27, 29, 59, 61, 62, 66]. Additionally, limiting prone positioning and encouraging supine or lateral positioning during sleep may prevent SUDEP given that positioning at seizure onset determines postictal body position [68, 81, 141, 142]. Whether counseling people with epilepsy to sleep on their backs will reduce risk is unclear due to natural turning during sleep throughout the night [143]. Nocturnal surveillance is also a protective factor against SUDEP and may be utilized in select individuals [62, 142]. Nocturnal supervision and listening devices can alert caregivers to a seizure, allowing them or medical personnel to administer rescue medication, provide cardiopulmonary resuscitation or tactile stimulation, or turn the person to the recovery position to prevent hypoxia and hypercapnia [16, 66, 140]. Seizure alert alarms and anti-suffocation pillows may be beneficial but have not been studied for SUDEP [144], while lattice pillows may reduce airway obstruction but are not validated for use in epilepsy [19, 140, 144]. Further studies are necessary to provide high-quality evidence regarding the role of nocturnal supervision [145].

Hospital Setting

Interventions within the hospital can reduce seizure duration, respiratory dysfunction, and EEG suppression [73]. Constant supervision in the epilepsy monitoring unit and associated oxygen saturation and electrocardiogram monitoring can alert clinicians to catalyze early intervention [140, 146]. Repositioning the individual from the prone position, oral suctioning, oxygen administration, prompt and regular ASM administration, and immediate resuscitation may mitigate direct and indirect factors that increase the SUDEP risk [81, 144]. Education of providers in the epilepsy monitoring unit and otherwise in care enables adequate early intervention to minimize cardiorespiratory dysfunction [73, 140].

Conclusion

SUDEP is the most common cause of epilepsy-related mortality in people with epilepsy. Unmodifiable and modifiable risk factors have been identified. Potential direct pathophysiological determinant includes altering

cardiorespiratory function, pulmonary impairment, electrocerebral shut-down, adenosine dysfunction, and genetic susceptibility. Methods to prevent SUDEP centers on increasing awareness broadly, addressing unmodifiable and modifiable risk factors, and enacting hospital protocols. Additional studies are necessary to comprehensively characterize risk factors and pathophysiology to develop evidence-based algorithms to minimize SUDEP.

Acknowledgements

JWS is based at the NIHR University College London Hospitals Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's Biomedical Research Centres' funding scheme. He receives support from the UK Epilepsy Society, the Dr. Marvin Weil Epilepsy Research Fund and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, Netherlands.

Declarations

Conflict of Interest

NAS has no conflicts to report. JWS has received personal fees from Eisai, Arvelle, UCB and Zogenix and grants from UCB and GW Pharmaceuticals outside the submitted work.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References and Recommended Reading

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*. 2010;51(5):883–90.
2. Ngugi AK, Kariuki S, Bottomley C, Kleinschmidt I, Sander J, Newton C. Incidence of epilepsy: a systematic review and meta-analysis. *Neurology*. 2011;77(10):1005–12.
3. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;88(3):296–303.
4. Zielihski JJ. Epilepsy and mortality rate and cause of death. *Epilepsia*. 1974;15(2):191–201.
5. Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. *Epilepsia*. 1980;21(4):399–412.
6. Cockerell OC, Hart Y, Sander JW, Goodridge D, Shorvon S, Johnson A. Mortality from epilepsy: results from a prospective population-based study. *The Lancet*. 1994;344(8927):918–21.
7. Nilsson L, Tomson T, Farahmand B, Diwan V, Persson P. Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy. *Epilepsia*. 1997;38(10):1062–8.
8. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol*. 2001;49(3):336–44.
9. Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. *The Lancet Neurology*. 2006;5(6):481–7.

10. Ding D, Wang W, Wu J, et al. Premature mortality in people with epilepsy in rural China: a prospective study. *The Lancet Neurology*. 2006;5(10):823–7.
11. Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med*. 2010;363(26):2522–9.
12. Hutchison A, Tobias M, Glover J, Wright C, Hetzel D, Fisher E. Australian and New Zealand Atlas of Avoidable Mortality. Public Health Information Development Unit; 2006.
13. Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. *Brain*. 2004;127(11):2427–32.
14. Hitiris N, Mohanraj R, Norrie J, Brodie MJ. Mortality in epilepsy. *Epilepsy Behav*. 2007;10(3):363–76.
15. Lhatoo SD, Sander JW. Cause-specific mortality in epilepsy. *Epilepsia*. 2005;46:36–9.
16. Langan Y, Nashef L, Sander J. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry*. 2000;68(2):211–3.
17. Téllez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Res*. 2005;65(1–2):101–15.
18. Watkins L, Shankar R. Reducing the risk of sudden unexpected death in epilepsy (SUDEP). *Curr Treat Options Neurol*. 2018;20(10):40.
19. Devinsky O. Sudden, unexpected death in epilepsy. *N Engl J Med*. 2011;365(19):1801–11.
20. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *The Lancet Neurology*. 2008;7(11):1021–31.
21. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *The Lancet*. 2011;378(9808):2028–38.
22. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia*. 1997;38:S6–8.
23. Annegers J. United States perspective on definitions and classifications. *Epilepsia*. 1997;38:S9–12.
24. Ficker DM, So E, Shen W, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology*. 1998;51(5):1270–4.
25. Tomson T, Walczak T, Sillanpää M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. *Epilepsia*. 2005;46:54–61.
26. Terrence CF, Wisotzkey HM, Perper JA. Unexpected, unexplained death in epileptic patients. *Neurology*. 1975;25(6):594–594.
27. Leestma JE, Kalelkar MB, Teas SS, Jay GW, Hughes JR. Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia*. 1984;25(1):84–8.
28. Jick S, Cole T, Mesher R, Tennis P, Jick H. Sudden unexplained death in young persons with primary epilepsy. *Pharmacoepidemiol Drug Saf*. 1992;1(2):59–64.
29. Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan. *Canada Epilepsia*. 1995;36(1):29–36.
30. Langan Y, Nolan N, Hutchinson M. The incidence of sudden unexpected death in epilepsy (SUDEP) in South Dublin and Wicklow. *Seizure*. 1998;7(5):355–8.
31. Nilsson L, Farahmand B, Persson P, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case control study. *The Lancet*. 1999;353(9156):888–93.
32. Walczak TS, Leppik IE, D’amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology*. 2001;56(4):519–525.
33. Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure*. 2003;12(7):456–64.
34. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. *Neurology*. 2017;89(2):170–7.
35. Tomson T, Sveinsson O, Carlsson S, Andersson T. Evolution over time of SUDEP incidence: A nationwide population-based cohort study. *Epilepsia*. 2018;59(8):e120–4.
36. Timmings P. Sudden unexpected death in epilepsy: a local audit. *Seizure*. 1993;2(4):287–90.
37. Klenerman P, Sander J, Shorvon S. Mortality in patients with epilepsy: a study of patients in long term residential care. *J Neurol Neurosurg Psychiatry*. 1993;56(2):149–52.
38. Nashef L, Fish D, Sander J, Shorvon S. Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral centre. *J Neurol Neurosurg Psychiatry*. 1995;58(4):462–4.
39. Nashef L, Fish D, Garner S, Sander J, Shorvon S. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia*. 1995;36(12):1187–94.
40. Derby LE, Tennis P, Jick H. Sudden unexplained death among subjects with refractory epilepsy. *Epilepsia*. 1996;37(10):931–5.
41. Leestma JE, Annegers JF, Brodie MJ, et al. Sudden unexplained death in epilepsy: observations from a large clinical development program. *Epilepsia*. 1997;38(1):47–55.
42. Annegers J, Coan SP, Hauser W, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia*. 2000;41(5):549–53.
43. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. *Am J Ment Retard*. 2000;105(4):229–35.
44. Racoosin JA, Feeney J, Burkhart G, Boehm G. Mortality in antiepileptic drug development programs. *Neurology*. 2001;56(4):514–9.
45. Vlooswijk M, Majoie H, De Krom M, Tan I, Aldenkamp A. SUDEP in the Netherlands: a retrospective study in a tertiary referral center. *Seizure*. 2007;16(2):153–9.
46. Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*. 1991;8(2):216–22.
47. Hennessy M, Langan Y, Elwes R, Binnie C, Polkey C, Nashef L. A study of mortality after temporal lobe epilepsy surgery. *Neurology*. 1999;53(6):1276–1276.
48. Nilsson L, Ahlbom A, Farahmand BY, Tomson T. Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia*. 2003;44(4):575–81.

49. Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. Mortality after epilepsy surgery. *Epilepsia*. 2005;46:49–53.
50. Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia*. 2018;59(3):562–72.
51. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. *Epilepsia*. 2018;59(3):555–61.
52. Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. *Ann Neurol*. 1999;46(1):45–50.
53. Group MRCADWS. Randomized study of antiepileptic drug withdrawal in patients in remission. *Lancet*. 1991;337(8751):1175–1180.
54. Donner EJ, Smith CR, Snead OC. Sudden unexplained death in children with epilepsy. *Neurology*. 2001;57(3):430–4.
55. Camfield P, Camfield C. Special considerations for a first seizure in childhood and adolescence. *Epilepsia*. 2008;49:40–4.
56. Shmuelly S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. *Epilepsy Behav*. 2016;64:69–74.
57. Mellor G, Raju H, de Noronha SV, et al. Clinical characteristics and circumstances of death in the sudden arrhythmic death syndrome. Circulation: Arrhythmia and Electrophysiology. 2014;7(6):1078–1083.
58. Devinsky O, Friedman D, Cheng JY, Moffatt E, Kim A, Tseng ZH. Underestimation of sudden deaths among patients with seizures and epilepsy. *Neurology*. 2017;89(9):886–92.
59. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. *Epilepsia*. 2011;52(6):1150–9.
60. Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. *Seizure*. 1999;8(6):347–52.
61. Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*. 1989;26(2):195–203.
62. Shankar R, Walker M, McLean B, et al. Steps to prevent SUDEP: the validity of risk factors in the SUDEP and seizure safety checklist: a case control study. *J Neurol*. 2016;263(9):1840–6.
63. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. *Epilepsy Behav*. 2007;10(1):138–41.
64. Langan Y, Nashef L, Sander J. Case-control study of SUDEP. *Neurology*. 2005;64(7):1131–3.
65. Young C, Shankar R, Palmer J, et al. Does intellectual disability increase sudden unexpected death in epilepsy (SUDEP) risk? *Seizure*. 2015;25:112–6.
66. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. *Neurology*. 2020;94(4):e419–29.
67. van der Lende M, Hesdorffer DC, Sander JW, Thijs RD. Nocturnal supervision and SUDEP risk at different epilepsy care settings. *Neurology*. 2018;91(16):e1508–18.
68. Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. *J Neurol Neurosurg Psychiatry*. 2016;87(4):402–13.
69. Abdel-Mannan O, Taylor H, Donner EJ, Sutcliffe AG. A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood. *Epilepsy Behav*. 2019;90:99–106.
70. Shankar R, Jalihal V, Walker M, et al. A community study in Cornwall UK of sudden unexpected death in epilepsy (SUDEP) in a 9-year population sample. *Seizure*. 2014;23(5):382–5.
71. Monté C, Arends J, Tan I, Aldenkamp A, Limburg M, De Krom M. Sudden unexpected death in epilepsy patients: risk factors: a systematic review. *Seizure*. 2007;16(1):1–7.
72. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Pharmacological treatment and SUDEP risk: A nationwide population-based case-control study. *Neurology*. 2020;
73. Jones LA, Thomas RH. Sudden death in epilepsy: Insights from the last 25 years. *Seizure*. 2017;44:232–6.
74. Aurlien D, Larsen JP, Gjerstad L, Taubøll E. Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: A nested, case-control study. *Epilepsia*. 2012;53(2):258–66.
75. French JA, Perucca E, Sander JW, et al. FDA safety warning on the cardiac effects of lamotrigine: An advisory from the Ad Hoc ILAE/AES Task Force. *Epilepsia Open*. 2021;6(1):45–8.
76. Nilsson L, Bergman U, Diwan V, Farahmand B, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. *Epilepsia*. 2001;42(5):667–73.
77. Timmings P. Sudden unexpected death in epilepsy: is carbamazepine implicated? *Seizure*. 1998;7(4):289–91.
78. Opeskin K, Burke M, Cordner SM, Berkovic SF. Comparison of antiepileptic drug levels in sudden unexpected deaths in epilepsy with deaths from other causes. *Epilepsia*. 1999;40(12):1795–8.
79. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis *Epilepsia*. 2012;53(2):249–52.
80. Tomson T, Hirsch LJ, Friedman D, et al. Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials. *Epilepsia*. 2013;54(1):135–40.
81. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *The Lancet Neurology*. 2013;12(10):966–77.
82. Lhatoo SD, Nei M, Raghavan M, et al. Nonseizure SUDEP: sudden unexpected death in epilepsy without preceding epileptic seizures. *Epilepsia*. 2016;57(7):1161–8.
83. Barot N, Nei M. Autonomic aspects of sudden unexpected death in epilepsy (SUDEP). *Clin Auton Res*. 2019;29(2):151–60.
84. Moseley B, Bateman L, Millichap JJ, Wirrell E, Panayiotopoulos CP. Autonomic epileptic seizures, autonomic effects of seizures, and SUDEP. *Epilepsy Behav*. 2013;26(3):375–85.
85. Nashef L, Walker F, Allen P, Sander J, Shorvon S, Fish D. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry*. 1996;60(3):297–300.

86. Bateman LM, Li C-S, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain*. 2008;131(12):3239–45.
87. Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns. *Epilepsia*. 2010;51(8):1359–64.
88. Opherck C, Coromilas J, Hirsch LJ. Heart rate and EKG changes in 102 seizures: analysis of influencing factors. *Epilepsy Res*. 2002;52(2):117–27.
89. Leutmezer F, Scherthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. *Epilepsia*. 2003;44(3):348–54.
90. Moseley BD, Wirrell EC, Nickels K, Johnson JN, Ackerman MJ, Britton J. Electrocardiographic and oximetric changes during partial complex and generalized seizures. *Epilepsy Res*. 2011;95(3):237–45.
91. Schuele S, Bermeo A, Alexopoulos A, et al. Video-electrographic and clinical features in patients with ictal asystole. *Neurology*. 2007;69(5):434–41.
92. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger C. Cardiac asystole in epilepsy: clinical and neurophysiologic features. *Epilepsia*. 2003;44(2):179–85.
93. Velagapudi P, Turagam M, Laurence T, Kocheril A. Cardiac arrhythmias and sudden unexpected death in epilepsy (SUDEP). *Pacing Clin Electrophysiol*. 2012;35(3):363–70.
94. Ronkainen E, Ansakorpi H, Huikuri H, Myllylä V, Isojärvi J, Korpelainen J. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 2005;76(10):1382–6.
95. Devinsky O. Effects of seizures on autonomic and cardiovascular function. *Epilepsy currents*. 2004;4(2):43–6.
96. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. *Nat Rev Neurol*. 2014;10(5):271.
97. Stein P, PK, Kleiger M, RE. Insights from the study of heart rate variability. *Annual review of medicine*. 1999;50(1):249–261.
98. Seyal M, Pascual F, Lee CYM, Li CS, Bateman LM. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. *Epilepsia*. 2011;52(11):2105–11.
99. Kato H, Menon AS, Slutsky AS. Mechanisms mediating the heart rate response to hypoxemia. *Circulation*. 1988;77(2):407–14.
100. Kara T, Narkiewicz K, Somers V. Chemoreflexes—physiology and clinical implications. *Acta Physiol Scand*. 2003;177(3):377–84.
101. Seyal M, Hardin KA, Bateman LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. *Epilepsia*. 2012;53(5):825–31.
102. Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures: intracranial EEG recordings in refractory temporal lobe epilepsy. *Epilepsia*. 2009;50(12):2557–62.
103. Shmueli S, Surges R, Sander JW, Thijs RD. Prone sleeping and SUDEP risk: the dynamics of body positions in nonfatal convulsive seizures. *Epilepsy Behav*. 2016;62:176–9.
104. Severson CA, Wang W, Pieribone VA, Dohle CI, Richerson GB. Midbrain serotonergic neurons are central pH chemoreceptors. *Nat Neurosci*. 2003;6(11):1139–40.
105. Richerson GB. Serotonergic neurons as carbon dioxide sensors that maintain pH homeostasis. *Nat Rev Neurosci*. 2004;5(6):449–61.
106. Buchanan GF, Richerson GB. Central serotonin neurons are required for arousal to CO₂. *Proc Natl Acad Sci*. 2010;107(37):16354–9.
107. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia*. 2012;53(2):253–7.
108. Phillipson EA. Control of breathing during sleep. *Am Rev Respir Dis*. 1978;118(5):909–39.
109. Douglas NJ, White DP, Weil JV, et al. Hypoxic ventilatory response decreases during sleep in normal men. *Am Rev Respir Dis*. 1982;125(3):286–9.
110. White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW. Hypoxic ventilatory response during sleep in normal premenopausal women. *Am Rev Respir Dis*. 1982;126(3):530–3.
111. Wiegand L, Zwillich CW, White DP. Sleep and the ventilatory response to resistive loading in normal men. *J Appl Physiol*. 1988;64(3):1186–95.
112. Billakota S, Odom N, Westwood AJ, Hanna E, Pack AM, Bateman LM. Sleep-disordered breathing, neuroendocrine function, and clinical SUDEP risk in patients with epilepsy. *Epilepsy Behav*. 2018;87:78–82.
113. Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology*. 2000;55(7):1002–7.
114. Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. *Neurology*. 2007;69(19):1823–7.
115. Foldvary-Schaefer N, Andrews ND, Pornsriniyom D, Moul DE, Sun Z, Bena J. Sleep apnea and epilepsy: Who's at risk? *Epilepsy Behav*. 2012;25(3):363–7.
116. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. *J Appl Physiol*. 2014;116(3):325–36.
117. Ali A, Wu S, Issa NP, et al. Association of sleep with sudden unexpected death in epilepsy. *Epilepsy Behav*. 2017;76:1–6.
118. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. *Ann Neurol*. 2010;68(6):787–96.
119. Surges R, Strzelczyk A, Scott CA, Walker MC, Sander JW. Postictal generalized electroencephalographic suppression is associated with generalized seizures. *Epilepsy Behav*. 2011;21(3):271–4.
120. Lee A, Wu S, Zhou X, Liebenthal J, Rose S, Tao JX. Periictal autonomic dysfunction and generalized postictal EEG suppression in convulsive seizures arising from sleep and wakefulness. *Epilepsy Behav*. 2013;28(3):439–43.
121. Moseley BD, So E, Wirrell EC, et al. Characteristics of postictal generalized EEG suppression in children. *Epilepsy Res*. 2013;106(1–2):123–7.
122. Patodia S, Paradiso B, Garcia M, et al. Adenosine kinase and adenosine receptors A1R and A2AR in temporal lobe

- epilepsy and hippocampal sclerosis and association with risk factors for SUDEP. *Epilepsia*. 2020;61(4):787–97.
123. Boison D. Adenosine dysfunction in epilepsy. *Glia*. 2012;60(8):1234–43.
 124. Shen HY, Li T, Boison D. A novel mouse model for sudden unexpected death in epilepsy (SUDEP): role of impaired adenosine clearance. *Epilepsia*. 2010;51(3):465–8.
 125. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. *Epilepsy Res*. 2016;128:43–7.
 126. Kim Y, Bravo E, Thirnbeck CK, et al. Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. *J Clin Investig*. 2018;128(3):1141–53.
 127. Bagnall RD, Crompton DE, Semsarian C. Genetic basis of sudden unexpected death in epilepsy. *Front Neurol*. 2017;8:348.
 128. Kuchenbuch M, Barcia G, Chemaly N, et al. KCNT1 epilepsy with migrating focal seizures shows a temporal sequence with poor outcome, high mortality and SUDEP. *Brain*. 2019;142(10):2996–3008.
 129. Johannesen KM, Gardella E, Scheffer I, et al. Early mortality in SCN8A-related epilepsies. *Epilepsy Res*. 2018;143:79–81.
 130. Friedman D, Thaler A, Thaler J, et al. mortality in isodicentric chromosome 15 syndrome: the role of SUDEP. *Epilepsy Behav*. 2016;61:1–5.
 131. Glasscock E. Genomic biomarkers of SUDEP in brain and heart. *Epilepsy Behav*. 2014;38:172–9.
 132. Louik J, Doumlele K, Hussain F, et al. Experiences with premorbid SUDEP discussion among participants in the North American SUDEP Registry (NASR). *Epilepsy Behav*. 2017;70:131–4.
 133. Xu Z, Ayyappan S, Seneviratne U. Sudden unexpected death in epilepsy (SUDEP): what do patients think? *Epilepsy Behav*. 2015;42:29–34.
 134. Friedman D, Donner EJ, Stephens D, Wright C, Devinsky O. Sudden unexpected death in epilepsy: knowledge and experience among US and Canadian neurologists. *Epilepsy Behav*. 2014;35:13–8.
 135. Waddell B, McColl K, Turner C, et al. Are we discussing SUDEP?—A retrospective case note analysis. *Seizure*. 2013;22(1):74–6.
 136. Miller WR, Young N, Friedman D, Buelow JM, Devinsky O. Discussing sudden unexpected death in epilepsy (SUDEP) with patients: practices of health-care providers. *Epilepsy Behav*. 2014;32:38–41.
 137. Gayatri NA, Morrall MC, Jain V, Kashyape P, Pysden K, Ferrie C. Parental and physician beliefs regarding the provision and content of written sudden unexpected death in epilepsy (SUDEP) information. *Epilepsia*. 2010;51(5):777–82.
 138. Long L, Cotterman-Hart S, Shelby J. To reveal or conceal? Adult patient perspectives on SUDEP disclosure. *Epilepsy Behav*. 2018;86:79–84.
 139. Radhakrishnan DM, Ramanujam B, Srivastava P, Dash D, Tripathi M. Effect of providing sudden unexpected death in epilepsy (SUDEP) information to persons with epilepsy (PWE) and their caregivers—Experience from a tertiary care hospital. *Acta Neurol Scand*. 2018;138(5):417–24.
 140. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? *Epilepsia*. 2013;54:23–8.
 141. Mahr K, Bergmann M-P, Kay L, et al. Prone, lateral, or supine positioning at seizure onset determines the postictal body position: A multicenter video-EEG monitoring cohort study. *Seizure*. 2020;76:173–8.
 142. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsy currents*. 2017;17(3):180–7.
 143. Tao JX, Sandra R, Wu S, Ebersole JS. Should the “Back to Sleep” campaign be advocated for SUDEP prevention? *Epilepsy Behav*. 2015;100(45):79–80.
 144. Rugg-Gunn F, Duncan J, Hjalgrim H, Seyal M, Bateman L. From unwitnessed fatality to witnessed rescue: Nonpharmacologic interventions in sudden unexpected death in epilepsy. *Epilepsia*. 2016;57:26–34.
 145. Maguire MJ, Jackson CE, Marson AG, Nevitt SJ. Treatments for the prevention of sudden unexpected death in epilepsy (SUDEP). *Cochrane Database of Systematic Reviews*. 2016;(7)
 146. Nobili L, Proserpio P, Rubboli G, Montano N, Didato G, Tassinari CA. Sudden unexpected death in epilepsy (SUDEP) and sleep. *Sleep Med Rev*. 2011;15(4):237–46.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.