JPPT | State of the Art Review

Sudden Unexpected Death in Epilepsy (SUDEP): A Review of Risk Factors and Possible Interventions in Children

Emily Wicker, PharmD and Justin W. Cole, PharmD

Sudden unexpected death in epilepsy (SUDEP) is a serious and devastating, yet poorly understood outcome in epilepsy. This review discusses the current knowledge and understanding of SUDEP in children and adolescents. Established risk factors for SUDEP include history of generalized tonic-clonic seizures and nocturnal seizures. Other proposed risk factors include the use of multiple antiseizure medications and poor medication adherence. Possible prevention strategies for SUDEP include improved medication adherence, surgical interventions, nighttime safety, seizure detection devices, and diet. Pediatric providers have a great opportunity to educate families about SUDEP, assess medication adherence, and provide families with tools to improve medication adherence and learn about SUDEP in children and adolescents with epilepsy. Future research in SUDEP aims to further understand the etiology and risk factors of SUDEP, while developing more intervention strategies to prevent SUDEP.

ABBREVIATIONS ASM, antiseizure medication; EMU, epilepsy monitoring unit; GTCS, generalized tonic-clonic seizure; STAR, Supporting Treatment Adherence Regimen; SUDEP, sudden unexpected death in epilepsy; VEEG, video electroencephalogram; VNS, vagus nerve stimulation

KEYWORDS anticonvulsants; child; epilepsy; medication adherence; seizure; sudden unexpected death in epilepsy

J Pediatr Pharmacol Ther 2021;26(6):556–564

DOI: 10.5863/1551-6776-26.6.556

Introduction

Sudden unexpected death in epilepsy (SUDEP) is a rare, but serious outcome in patients with epilepsy. The unexpected nature of SUDEP, especially in children and adolescents, has significant impacts on friends, family, and caregivers. This review will summarize the current literature and provide practical recommendations for health care providers as they care for pediatric patients with epilepsy.

Definition. SUDEP is defined as a "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death."[1] SUDEP can be further classified on the basis of whether the patient was successfully resuscitated after the event, whether an autopsy confirmed diagnosis, and whether comorbid conditions contributed to death (Table 1).[1] However, these classifications can be difficult to apply to individual cases, leading to challenges when estimating incidence of SUDEP.[2]

Incidence. Owing to the rarity of SUDEP cases, varying methodologic approaches, and heterogeneous patient populations, the reported incidence rate of SUDEP in children varies from 0.22 to 1.11 per 1000 person-years.[3-9] SUDEP occurs less commonly in children than adults, with the incidence in adults ranging from 0.35 to 6 per 1000 person-years.[3] Table 2 summarizes studies reporting incidence rates of SUDEP in various pediatric cohorts.

Etiology. The etiology of SUDEP is poorly understood but may involve dysregulation of the cardiac, respiratory, and autonomic nervous systems (Figure). Structural and functional changes within the central nervous system may be involved, including brain volume loss in the brainstem and temporal lobe.[10,11] Studies from epilepsy monitoring units (EMUs) are particularly helpful in elucidating possible etiologies for SUDEP because of the difficulty of capturing these events. The MORTEMUS study by Ryvlin et al[12] compiled retrospective data from 147 EMUs resulting in 16 SUDEP cases and 9 near-SUDEP cases in patients 10 to 62 years of age. Through video electroencephalogram (VEEG) monitoring, all of the SUDEP cases experienced a generalized tonic-clonic seizure (GTCS) prior to cardiorespiratory arrest. In 10 of these cases, patients developed rapid breathing in the immediate postictal phase followed by generalized VEEG suppression and the development of bradycardia, apnea, and asystole.[12] This study suggests that many SUDEP cases begin with a seizure event followed by cardiorespiratory compromise. Pursuing this hypothesis, Singh et al[13] used VEEG, pulse-oximetry, electrocardi-

Table 1. SUDEP Classifications[1]

Classification	Definition
Definite SUDEP	Meets full definition of SUDEP with confirmed autopsy
Definite SUDEP plus	Meets full definition of SUDEP, but comorbid condition is contributor to death
Probable SUDEP	Meets full definition of SUDEP, but no autopsy is performed
Probable SUDEP plus	Meets full definition of SUDEP, but comorbid condition is contributor to death and no autopsy is performed
Possible SUDEP	Death could have been caused by SUDEP or other cause
Near-SUDEP	A patient who is resuscitated after SUDEP event
Near-SUDEP plus	A patient who is resuscitated after SUDEP event with other contributing cause

SUDEP, sudden unexpected death in epilepsy

ography, and respiratory inductance plethysmography data from an EMU to study risk factors leading to cardiopulmonary abnormalities following seizures in 26 patients aged 2 to 20 years. This study identified that ictal cardiopulmonary abnormalities, including apnea and bradycardia, are common in children with epilepsy. Ictal apnea and bradycardia were associated with male sex, localization-related epilepsy, increased seizure duration, and increased number of antiseizure medications (ASMs).[13]

Several case reports have analyzed occurrences of SUDEP and near-SUDEP not associated with epileptic events, both in a child and adults.[14,15] Given the heterogeneous nature of the data and the complex physiologic interplay of the autonomic, cardiac, and respiratory systems, it is likely that SUDEP cases may arise from a variety of etiologic phenomena.

Risk Factors. A number of risk factors have been identified for SUDEP. We will discuss these risk factors in the following categories: epilepsy type and severity, pharmacologic treatment, and genetics.

The predominant risk factor for SUDEP is a history of GTCS. Patients experiencing 3 or more GTCSs per year are at higher risk.[3,16] Of those for whom seizure type was reported, 53 of 60 (88%) patients experienced GTCs with an average of 16.3 GTCSs per month.[3] A separate Swedish case-control study, which included 225 cases of definite or probable SUDEP in patients 4 to 92 years of age, found that patients with a history of GTCs had a 10-fold increased risk of SUDEP.[17] Patients who experienced 1 to 3 GTCSs in the previous year had a 22-fold increase in SUDEP risk, while patients with 4 to 10 GTCSs in the previous year had a 32-fold increase in SUDEP risk.[17]

Other disease-related risk factors for SUDEP include onset of epilepsy in childhood or adolescence, symptomatic epilepsy, nocturnal seizures, and intellectual impairment or developmental delay.[3,7,17-21] Patients with onset of epilepsy at 0 to 15 years of age have a 7.7 times higher risk of SUDEP compared with those with onset of epilepsy at 45 years of age or later.[3] In another study, patients with an onset of epilepsy before 16 years of age had a 1.72-fold increased risk for SUDEP compared with those with an onset of epilepsy at 16 to 60 years of age.[18] In a cohort of 154 patients with SUDEP compared with living age-matched controls, nocturnal seizures were associated with a 2.6-fold increased risk for SUDEP after controlling for other risk factors.[19] Any history of nocturnal GTCS was associated with a 9-fold increased risk of SUDEP, while nocturnal GTCSs in the past year were associated with a 15-fold increased risk of SUDEP.[17]

While developmental delay and intellectual impairment have been proposed as risk factors, few studies have evaluated whether intellectual disability is an independent risk factor for SUDEP. Abdel-Mannan et al[3] noted that 33 (45%) of the evaluated SUDEP cases had developmental delay or intellectual impairment.[3] However, 14 children in this study were diagnosed with epileptic encephalopathies known to be associated with intellectual impairment, and etiology was not known for 27 children.[3] Because the incidence of epilepsy is known to increase in children with more profound intellectual impairment, it is difficult to determine if this is associated with an increased risk of SUDEP.[22]

Systematic reviews of case-control studies have found that patients receiving more than 1 ASM or experiencing changes in their ASM regimen 3 to 5 times per year were more likely to die of SUDEP.[7,18,21] This relationship could be confounded because patients with uncontrolled or treatment-resistant epilepsy are more likely to have more complicated medication therapy. A case-control study also suggests an association between subtherapeutic drug concentrations and SUDEP because 78 of the 91 patients who died from SUDEP had subtherapeutic drug concentrations, while only 8 of 91 control patients had subtherapeutic drug concentrations ($p < 0.0001$).[23] Patients not actively treated with ASMs may also be at higher risk.[16]

Multiple studies have identified genetic risk factors associated with an increased risk for SUDEP. Several genes have been associated with both an increased risk for specific seizure diagnoses and SUDEP, which are summarized in Table 3.[24-26] No specific genes have been associated with a decreased risk of SUDEP. However, patients with idiopathic epilepsy, which is classically understood to be genetic in origin, were disproportionately underrepresented in one study, suggesting that SUDEP may occur less frequently in these patients.[3] Genetic associations not directly correlated with epilepsy may

Table 2. Incidence of SUDEP in Pediatric Patients

Study	Methodology (Setting)	Population	Incidence
Nickels[4]	Retrospective medical record review (Olmsted County, MN)	Children birth to 17 years of age with new-onset epilepsy from 1980–2009	0.22 per 1000 person-years
Nesbitt[5]	Retrospective clinical and death certificate review (United Kingdom)	2 samples: Children <18 years of age with epilepsy who died between 1989 and 2005 Children 28 days to 17 years of age who died in 2006	0.65 per 1000 person-years
Keller[8]	Retrospective review from Canadian Pediatric Surveillance Program, Canadian Pediatric Epilepsy Network, and Ontario Forensic Pathology Service (Ontario, Canada)	Children <18 years of age who died of suspected SUDEP in 2014–2015	1.11 per 1000 person-years

SUDEP, sudden unexpected death in epilepsy

Table 3. Genes Associated With Seizure Disorders and Increased Risk for SUDEP

Gene[24,25]	Molecular Description[26]	Associated Seizure Disorders[26]
DEPDC5	DEP domain–containing protein 5 involved in G-protein signaling; mTOR regulation	FFEVF, ADNFLE, FMTLE, ADEAF, infantile spasms
dup15q idic(15)	Isodicentric chromosome 15	Infantile spasms
KCNT1	Sodium-activated potassium channel[9]	Epilepsy of infancy with migrating focal seizures
LGI1	Leucine-rich glioma inactivated protein	ADEAF
SCN1A	Sodium voltage-gated channel alpha subunit 1	GEFS+, ICE-GTCS, intractable infantile partial seizures, MAE, SMEI, DS, simple febrile seizures
SCN2A	Sodium voltage-gated channel alpha subunit 2	Benign neonatal infantile epilepsy
SCN8A	Sodium voltage-gated channel alpha subunit 8	Lennox-Gastaut syndrome, West syndrome, DS

ADEAF, autosomal dominant epilepsy with auditory features; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; DS, Dravet syndrome; FFEVF, familial focal epilepsy with variable foci; FMTLE, familial mesial temporal lobe epilepsies; GEFS+, generalized epilepsy with febrile seizures plus; ICE-GTCS, intractable childhood epilepsy with generalized tonic-clonic seizures; MAE, myoclonic astatic epilepsy; SMEI, severe myoclonic epilepsy in infancy

also play a role. Genes associated with cardiac disorders, including cardiomyopathies and long QT syndrome, have been identified as possible risk factors for SUDEP.[24-26] Variants of these genes could impact sodium and potassium ion channels located in both the nervous system and heart, possibly leading to a correlation with seizures and cardiac arrest.[24] Lastly, variants in genes that regulate opioid signaling pathways, glutamate, and gamma aminobutyric acid in neurotransmission may also be associated with SUDEP.[27]

Prevention

Medication Adherence. Because the risk of SUDEP increases with the frequency of GTCS, achieving effective seizure control could reduce a patient's risk of SUDEP. Along with rational treatment selection and optimization of therapy as quickly as the patient will tolerate, improved medication adherence may reduce the risk of SUDEP by increasing seizure control.[28-30]

Patterns of medication adherence have been defined in children diagnosed with epilepsy. The mean adherence rate within the first month of treatment following epilepsy diagnosis has been reported as 79.4%.[31] In another study of pediatric adherence for the first 6 months of treatment following epilepsy diagnosis, near-perfect adherence was achieved by only 42% of children.[32] Thirteen percent of patients were non-adherent.[32] At 1 year 26.6% of patients were not taking their prescribed ASM.[33] However, these studies all excluded patients with significant developmental disorders or other co-

Table 4. Recommendations from the American Academy of Neurology and American Epilepsy Society SUDEP Guidelines[55]

Recommendation
Pediatrics: Clinicians caring for children with epilepsy should inform the children's parents or guardians that: There is a rare risk of SUDEP. In 1 year, SUDEP typically affects 1 in 4500 children with epilepsy; in other words, annually, 4499 of 4500 children will not be affected by SUDEP.
Adults: Clinicians should inform adult persons with epilepsy that: There is a small risk of SUDEP. In 1 year, SUDEP typically affects 1 in 1000 adults with epilepsy; in other words, annually, 999 or 1000 adults will not be affected by SUDEP.
For persons with epilepsy who continue to experience GTCS, clinicians should continue to actively manage epilepsy therapies to reduce seizure occurrences and the risk of SUDEP while incorporating patient preferences and weighing the risks and benefits of any new approach.
For persons with frequent GTCS and nocturnal seizures, clinicians may advise selected patients and families, if permitted by their individualized epilepsy and psychosocial circumstances, to use nocturnal supervision or other nocturnal precautions, such as the use of a remote listening device, to reduce SUDEP risk.
Clinicians should inform patients with epilepsy that seizure freedom, particularly freedom from GTCS (which is more likely to occur with medication adherence), is strongly associated with a decreased risk of SUDEP.

GTCS, generalized tonic-clonic seizure; SUDEP, sudden unexpected death in epilepsy

morbidities requiring daily medication use, which limits generalizability to children at a higher risk of SUDEP.[31-33]

Single-parent homes,[31] lower socioeconomic status,[31-34] poorer family communication and problem-solving skills,[34] and greater parent fears and stressors[34] have been correlated with poorer adherence in children with epilepsy. White coat adherence, the phenomenon of increased adherence in the days prior to clinic visits, has been observed in pediatric patients with epilepsy.[35] Through the Pediatric Epilepsy Medication Self-Management Questionnaire parents of children ages 2 to 12 years with new-onset epilepsy identified forgetting to give the medication and their child's disliking the taste as the most common barriers to medication adherence.[36] Similarly, higher socioeconomic status, increased incidence of side effects, fewer adherence barriers, greater caregiver responsibility, and lower family conflict are associated with improved medication adherence in adolescents.[37,38]

To date, no studies have directly correlated improved medication adherence with lower rates of SUDEP. However, this may be due to methodologic constraints of such research. Regardless, medication adherence should be promoted in all children diagnosed with epilepsy. Important steps in managing non-adherence include screening for risk factors for non-adherence, identification of reasons for non-adherence, and use of strategies to combat those factors.[39] Potential strategies include simplifying drug regimens, epilepsy and medication education, addressing adverse drug reactions, and assisting with memory aids.[39] Patients who achieve seizure freedom with their medication may become less strict about their medication adherence; therefore, frequent discussions about medication adherence with patients are important.[40]

One proposed and studied method to improve medication adherence in pediatric epilepsy is the Supporting Treatment Adherence Regimen (STAR) intervention.[41,42] The STAR intervention consists of 4 sessions focused on providing information about epilepsy and problem-solving for identified barriers including behavioral contracts and frequent follow-up.[41,42] The authors noted that children were included in the problem-solving process in age-appropriate ways including brainstorming ideas for improving adherence and choosing rewards for good adherence.[41] Though this pilot study was limited by a small sample size, families in the treatment group demonstrated an average improved adherence of 31.5%, while families in the control group had an average improved adherence of 9.3%.[41] The follow-up study found that the STAR method significantly improved patient adherence when compared with the control group following the third and fourth sessions.[42] However, at 3-month follow-up there was not a statistically significant difference in the adherence rates between groups.[42] These findings highlight the need for continual follow-up and discussion of adherence with patients and their families. Further research into the STAR method is forthcoming.[43]

Another proposed method for improving medication adherence includes the use of text messaging or mobile application–based reminders. A pilot study of the use of technologic reminders for teenagers demonstrated that parents and teenagers found these interventions beneficial although significant changes in adherence were not seen.[44] While improving medication adherence could decrease seizure frequency and ultimately the risk of SUDEP in children, more research is needed to evaluate the impact of interventions to increase medication adherence and on SUDEP risk.

Non-pharmacologic Approaches. ***Surgical Intervention***. For patients with treatment-refractory epilepsy, surgical intervention is often helpful in improving seizure control. Improved seizure control following epilepsy surgery is correlated with lower mortality overall, and potentially a decreased risk of SUDEP.[45-47] The degree to which surgical interventions impact mortality in epilepsy may be dependent on epilepsy type and specific

surgical intervention. In a recent analysis of primarily adult patients with treatment-resistant focal epilepsy, the standardized mortality ratio for SUDEP was 1.9 per 1000 person-years in the surgery group compared with 4.6 per 1000 person-years in the comparator group.[45] All SUDEP cases in both groups occurred in those with seizures arising from one or both temporal lobes, potentially highlighting the importance of temporal lobe epilepsy and SUDEP risk.[45] In a separate study of patients who had undergone temporal lobe epilepsy surgery, 6 cases of SUDEP were reported in 299 patients over the study period, translating to an incidence of 1 in 455 person-years.[48] The small sample sizes limit interpretation of these studies, and more data are needed to fully elucidate the impact of various epilepsy surgery approaches on SUDEP risk.

Vagus nerve stimulation (VNS) therapy has also been reported to decrease the risk for SUDEP. In an analysis of 40,443 patients receiving VNS therapy, age-adjusted SUDEP rates significantly decreased to 2.47 per 1000 person-years in the first 2 years following implantation.[49] The reported SUDEP was 1.68 per 1000 person-years during years 3 to 10 following VNS.[49] Of note, the reported rates of SUDEP in this surgical cohort are higher owing to the increased incidence of treatment-resistant epilepsy. Data on the rates of SUDEP following other epilepsy surgical procedures including corpus callosotomy and deep brain stimulation are lacking.

Sleep Safety and Nighttime Supervision. Sleeping in the prone position has been associated with SUDEP, as one cohort study identified that 85 of 97 (87.6%) patients who were asleep when SUDEP occurred were in the prone position.[50] Because most SUDEP incidents happen during sleep, night-time supervision and the use of lattice pillows have been suggested as measures to prevent SUDEP.[28] Lattice pillows are constructed with mesh designed to increase air flow when someone is sleeping in the prone position. One study of patients in an EMU showed that prompt response may improve outcomes when 7 patients were resuscitated from near-SUDEP because Cardiopulmonary Resuscitation was initiated within 3 minutes of the event.[12] This also highlights the importance of providing parents and caregivers with information about SUDEP and opportunities to learn basic life support.

Diet. Another intervention for pediatric patients with treatment-resistant epilepsy is the ketogenic diet. Research on the ketogenic diet has shown seizure reduction in pediatric patients, but there are many adverse effects that can make the ketogenic diet intolerable.[51] A systematic review and meta-analysis completed by Rezaei et al[52] concluded that a modified Atkins diet had similar efficacy as the ketogenic diet with reduced adverse effects. For patients with treatment-resistant epilepsy, the ketogenic diet or modified Atkins diet may be considered to decrease seizure burden and associated complications or concerns including possibly the risk of SUDEP.

Table 5. Key Takeaways

The reported incidence of SUDEP in children and adolescents ranges from 0.2 to 1.1 per 1000 person-years.
Generalized tonic-clonic seizures are the greatest known risk factor for SUDEP.
The risk of SUDEP should be discussed with pediatric patients diagnosed with epilepsy along with their caregivers.
Improved seizure control through medication adherence and non-pharmacologic interventions including vagal nerve stimulation and diet modifications could reduce patients' risk of SUDEP.
Research should continue to explore the etiology of and effective preventative measures for SUDEP.

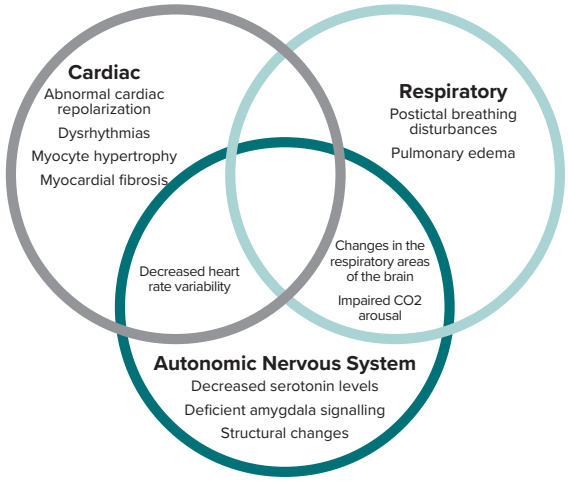
SUDEP, sudden unexpected death in epilepsy

Patient-Provider Communication

The Institute of Medicine, in its publication *Epilepsy Across the Spectrum*, mentions SUDEP as a basic educational need of all individuals with epilepsy.[53] Table 4 displays the recommendations from the American Academy of Neurology and American Epilepsy Society SUDEP Guidelines concerning SUDEP communication.[54] Most parents express a desire to discuss SUDEP in person with their neurologist upon diagnosis and receive additional resources to help them process this information.[55,56] Patient resources are available through organizations such as the Epilepsy Foundation and Danny Did Foundation. Discussions should also include the known modifiable risk factors of SUDEP, namely optimization of drug therapy to reduce seizure occurrence.[57] There is debate about when to tell children and their caregivers about SUDEP. Owing to various levels of maturity, development, and independence there is not a defined age when children should be told.[56] We suggest that education should be provided to parents or caregivers soon after diagnosis, and that timing of communication with the child be part of a shared decision-making partnership with the caregivers.

While most patients desire to know about SUDEP, only 8.7% to 29% of health care professionals in any setting report discussions of SUDEP with all or most of their patients.[58] Among pediatricians, reasons reported for not discussing SUDEP were a lack of provider knowledge and assumption that specialists such as neurologists would discuss SUDEP with their patients.[59] One survey of pediatric primary care providers demonstrated that 85.6% of providers were not familiar with SUDEP.[59] Another reason that providers may not discuss SUDEP with their patients is the belief that their patients are not at risk.

Figure. Proposed pathophysiologic mechanisms associated with SUDEP by organ system.



SUDEP, sudden unexpected death in epilepsy

A SUDEP and seizure safety checklist has been developed to aid providers in their discussions with patients, but thus far it has been used only in adult patients.[60] The SUDEP-7 Inventory was developed to help identify patients at highest risk for SUDEP, but a case-control study of patients ages 10 to 73 years found no statistically significant difference in scores between the cases and controls ($p = 0.39$).[61] Others have suggested using technology within electronic medical records to identify patients at risk for SUDEP in order to prompt providers to have SUDEP discussions with their patients.[62] A clinical trial of a computerized clinical support program to remind providers to discuss SUDEP with pediatric patients and their caregivers has been conducted and results are pending.[63] Regardless, there is a discrepancy between information that patients desire to receive about SUDEP and what they are presented by their health care providers.[64] Providers should be prepared to discuss SUDEP with their patients in an accurate and sensitive manner.[65]

Future Research

Etiology and Risk Factors. Research continues to identify the etiology and risk factors associated with SUDEP. A North American SUDEP registry has been established to include data from medical records and family interviews of patients who die of SUDEP to better characterize the incidence and risk factors of SUDEP.[66] Another case-control study aims to further understand the risk factors associated with SUDEP, including whether ASMs and nighttime supervision modify this risk.[67] Another clinical trial is testing the hypothesis of a relationship between SUDEP-7 scores and neural-circulatory control to help identify patients at risk of SUDEP.[68] Two registered clinical trials are reviewing carbon dioxide and SpO_2 levels and their association with SUDEP.[69,70] Additionally, the Institute of Medicine recommends prevention studies in high-risk individuals to further understand risk factors for SUDEP.[53]

Medication Therapy. There are several novel pharmacotherapeutic agents that may decrease the risk of SUDEP. Selective serotonin receptor inhibitors have been proposed as a possible therapy to prevent SUDEP by improving seizure control and reducing postictal central apnea.[71] This approach has been hypothesized owing to observed similarities between SUDEP and sudden infant death syndrome, which is associated with changes in the serotonergic system.[72] A phase 2 clinical trial is testing the impact of fluoxetine on minute ventilation during hypercapnic ventilatory response.[73] The use of naloxone immediately following a GTCS in an effort to increase postictal oxygen saturation is also being studied.[74] Any impact of these agents will require further analysis in the pediatric population, because these studies do not include pediatric patients.

Wearables and Other Technologies. Many watches and bed alarms are being tested and developed.[75-78] These devices could aid in the understanding of SUDEP and help to identify biomarkers while also measuring the frequency of seizures and impact of therapy.[49] One challenge is creating a technology with both the specificity and sensitivity to accurately detect potential SUDEP events based on physiologic parameters.[78] The 2019 Prevent21 Summit, a summit held in the United Kingdom focused on SUDEP prevention, recommended that all technologic alarms are only one part of minimizing the risk of SUDEP, because while monitoring and recording seizures is valuable, in order to help prevent SUDEP someone must be available to intervene when a seizure occurs.[79]

Conclusion

While many unknowns about SUDEP remain, health care professionals can provide evidence-based information about SUDEP to children and adolescents with epilepsy and their caregivers (Table 5). Health care professionals should work with families to reduce SUDEP risk factors by supporting medication adherence and discussing other treatment options including surgery and dietary interventions. As we await future research further defining the etiology, risk factors, and prevention measures for SUDEP, health care professionals should ensure that families are informed about the risks of SUDEP and steps they can take to help reduce their risk of SUDEP.

Article Information

Affiliations. Department of Pharmacy Practice (EW, JWC), Cedarville University School of Pharmacy, Cedarville, OH

Correspondence. Justin W. Cole, PharmD; jwcole@cedarville.edu

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Submitted. August 28, 2020

Accepted. December 3, 2020

References

1. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia*. 2012;53(2):227–233.
2. Devinsky O, Bundock E, Hesdorffer D, et al. Resolving ambiguities in SUDEP classification. *Epilepsia*. 2018;59(6):1220–1233.
3. 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.
4. Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30 year population-based study in Olmsted County, MN. *Epilepsia*. 2012;53(12):2164–2171.
5. Nesbitt V, Kirkpatrick M, Pearson G, et al. Risk and causes of death in children with a seizure disorder. *Dev Med Child Neurol*. 2012;54(7):612–617.
6. Abdel-Mannan O, Hughes E, Dunkley C. Epilepsy deaths in children: improvements driven by data and surveillance in pediatrics. *Epilepsy Behav*. 2020;103(pt B):106493. doi:10.1016/j.yebeh.2019.106493
7. DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: risk factors, biomarkers, and prevention. *Acta Neurol Scand*. 2019;139:220–230.
8. Keller AE, Whitney R, Li SA, et al. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology*. 2018;91(2):e107–e111.
9. 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.
10. Allen LA, Harper RM, Lhatoo S, et al. Neuroimaging of sudden unexpected death in epilepsy (SUDEP): insights from structural and resting-state functional MRI studies. *Front Neurol*. 2019;10:185. doi: 10.3389/fneur.2019.00185
11. Mueller SG, Bateman LM, Laxer KD. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. *Neuroimage Clin*. 2014;5:208–216.
12. Ryvlin P, Nashet L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol*. 2013;12(10):966–977.
13. Singh K, Katz ES, Zarowski M, et al. Cardiopulmonary complications during pediatric seizures: a prelude to understanding SUDEP. *Epilepsia*. 2013;54(6):1083–1091.
14. Lhatoo SD, Nei M, Raghavan M, et al. Nonseizure SUDEP: sudden unexpected death in epilepsy without preceding epileptic seizures. *Epilepsia*. 2016;57(7):1161–1168.
15. Ba-Armah DM, Donner EJ, Ochi A, et al. "Saved by the bell": near SUDEP during intracranial EEG monitoring. *Epilepsia Open*. 2018;3(1):98–102.
16. DeGiorgio CM, Markovic D, Mazumder R, Moseley BD. Ranking the leading risk factors for sudden unexpected death in epilepsy. *Front Neurol*. 2017;8:473. doi:10.3389/fneur.2017.00473
17. Sveinsson O, Andersson T, Mattsson P, et al. Clinic risk factors in SUDEP: a nationwide population-based case-control study. *Neurology*. 2020;94(4):e419–e429.
18. Hesdorffer DC, Tomson R, Benn E, et al. Combined analysis of risk factors for SUDEP. *Epilepsia*. 2011;52(6):1150–1159.
19. Lamberts RJ, Thijs RD, Laffan A, et al. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia*. 2012;53(2):253–257.
20. Surges R, Sperling MR, DeGiorgio CM. Sudden unexpected death in epilepsy: bio-markers, mechanisms, risk identification and prevention. *Front Neurol*. 2019;10:1277. doi:10.3389/fneur.2019.01277
21. Saxena A, Jones L, Shankar R, et al. Sudden unexpected death in epilepsy in children: a focused review of incidence and risk factors. *J Neurol Neurosurg Psychiatry*. 2018;89(10):1064–1070.
22. Lhatoo SD, Sander WAS. The epidemiology of epilepsy and learning disability. *Epilepsia*. 2001;42(suppl 1):6–9.
23. Hughes JR. A review of sudden unexpected death in epilepsy: prediction of patients at risk. *Epilepsy Behav*. 2009;14(2):280–287.
24. Chahal CAA, Salloum MN, Alahdab F, et al. Systematic review of the genetics of sudden unexpected death in epilepsy: potential overlap with sudden cardiac death and arrhythmia-related genes. *J Am Heart Assoc*. 2020;9(1):3012264. doi:10.1161/JAHA.119.012264
25. Coll M, Oliva A, Grassi S, et al. Update on the genetic basis of sudden unexpected death in epilepsy. *Int J Mol Sci*. 2019;20(8):1979. doi:10.3390/ijms20081979
26. Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle; 1993–2020. Accessed August 7, 2020. https://www.ncbi.nlm.nih.gov/books/NBK1116
27. Friedman D, Kannan K, Faustin A, et al. Cardiac arrhythmia and neuroexcitability gene variants in resected brain tissue from patients with sudden unexpected death in epilepsy (SUDEP). *NPJ Genom Med*. 2018;3:9. doi:10.1038/s41525-018-0048-5
28. Verma A, Kumar A. Sudden unexpected death in epilepsy: some approaches to prevent it. *J Neuropsychiatry Clin Neurosci*. 2015;27(1):e28–e31
29. Modi AC, Rausch JR, Glauser TA. Early pediatric antiepileptic drug nonadherence is related to lower long-term seizure freedom. *Neurology*. 2014;82(8):671–673.
30. Modi AC, Wu YP, Rausch JR, et al. Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes. *Neurology*. 2014;83(22):2085–2090.
31. Modi AC, Morita DA, Glauser TA. One-month adherence in children with new-onset epilepsy: white-coat compliance does not occur. *Pediatrics*. 2008;121(4):e961–e966.
32. Modi AC, Rausch JR, Glauser MD. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA*. 2011;305(16):1669–1676.

33. Aylward BS, Rausch JR, Modi AC. An examination of 1-year adherence and persistence rates to antiepileptic medication in children with newly diagnosed epilepsy. *J Pediatr Psychol*. 2015;40(1):66–74.
34. Loiselle K, Rausch JR, Modi AC. Behavioral predictors of medication adherence trajectories among youth with newly diagnosed epilepsy. *Epilepsy Behav*. 2015;50:103–107.
35. Modi AC, Ingerski LM, Rausch JR, et al. White coat adherence over the first year of therapy in pediatric epilepsy. *J Pediatr*. 2012;161(4):695–699.
36. Ramsey RR, Zhang N, Modi AC. The stability and influence of barriers to medication adherence on seizure outcomes and adherence in children with epilepsy over 2 years. *J Pediatr Psychol*. 2018;43(2):122–132.
37. Smith AW, Mara CA, Modi AC. Adherence to antiepileptic drugs in adolescents with epilepsy. *Epilepsy Behav*. 2018;80:307–311.
38. Holbein CE, Smith AW, Peugh J, Modi AC. Allocation of treatment responsibility in adolescents with epilepsy: associations with cognitive skills and medication adherence. *J Pediatr Psychol*. 2019;44(1):72–83.
39. Brodtkorb E, Samsonsen C, Sund JK, et al. Treatment non-adherence in pseudo-refractory epilepsy. *Epilepsy Res*. 2016;122:1–6.
40. Verducci C, Hussain F, Donner E, et al. SUDEP in the North American SUDEP registry: the full spectrum of epilepsies. *Neurology*. 2019;93(3):e227–e236.
41. Modi AC, Guilfoyle SM, Rausch J. Preliminary feasibility, acceptability, and efficacy of an innovative adherence intervention for children with newly diagnosed epilepsy. *J Pediatr Psychol*. 2013;38(6):605–616.
42. Modi AC, Guilfoyle SM, Mann KA, Rausch JR. A pilot randomized controlled clinical trial to improve antiepileptic drug adherence in young children with epilepsy. *Epilepsia*. 2016;57(3):e69–e75.
43. Modi AC, Glauser TA, Guilfoyle SM. Supporting treatment adherence regimens in young children with epilepsy and their families: trial design and baseline characteristics. *Contemp Clin Trials*. 2020;90:105959. doi:10.1016/j.cct.2020.105959
44. Modi AC, Mann KA, Urso L, Peugh J. Preliminary feasibility and efficacy of text messaging and application-based adherence interventions in adolescents with epilepsy. *Epilepsy Behav*. 2016;63:46–49.
45. Casadei CH, Carson KW, Mendiratta A, et al. All-cause mortality and SUDEP in a surgical epilepsy population. *Epilepsy Behav*. 2020;108:107093. doi:10.1016/j.yebeh.2020.107093
46. Sperling MR, Feldman H, Kinman J, et al. Seizure control and mortality in epilepsy. *Ann Neurol*. 1999;46(1):45–50.
47. Sperling MR. Sudden unexplained death in epilepsy. *Epilepsy Curr*. 2001;1(1):21–23.
48. Hennessy MJ, Langan Y, Elwes RDC, et al. A study of mortality after temporal lobe epilepsy surgery. 1999;53(6):1276–1283.
49. 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):562–572.
50. Ali A, Wu S, Issa NP, et al. Association of sleep with sudden unexpected death in epilepsy. *Epilepsy Behav*. 2017;76:1–6.
51. Martin-McGill KJ, Jackson CF, Bresnahan R, et al. Ketogenic diets for drug-resistant epilepsy (review). *Cochrane Database Syst Rev*. 2018;11(11):CD001903. doi:10.1002/14651858.CD001903.pub4
52. Rezael S, Abdurahman AA, Saghazadeh A, et al. Short-term and long-term efficacy of classical ketogenic diet and modified Atkins diet in epilepsy and adolescents with epilepsy: a systematic review and meta-analysis. *Nutr Neurosci*. 2019;22(5):317–334.
53. Institute of Medicine. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. Washington, DC: The National Academies Press; 2012.
54. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. *Neurology*. 2017;88(17):1674–1680.
55. Collard SS, Regmi P. Qualitative insights into the feelings, knowledge, and impact of SUDEP: a narrative synthesis. *Epilepsy Behav*. 2019;94:20–28.
56. Ramachandrannair R, Jack SM, Meaney BF, Ronen GM. SUDEP: what do parents want to know? *Epilepsy Behav*. 2013;29(3):560–564.
57. Watkins L, Shankar R, Sander JW. Identifying and mitigating sudden unexpected death in epilepsy (SUDEP) risk factors. *Expert Rev Neurother*. 2018;18(4):265–274.
58. Cooper K, Kirkpatrick P, Brand C, et al. Discussing sudden unexpected death in epilepsy with children and young people with epilepsy and their parents/carers: a mixed methods systematic review. *Seizure*. 2020;78:159–167.
59. Berl MM, Goodkin HP, Kroner BL, et al. Sudden death in epilepsy: knowledge among pediatric providers. *J Pediatr*. 2017;188:291-293.
60. Shankar R, Ashby S, McLean B, Newman C. Bridging the gap of risk communication and management using the SUDEP and seizure safety checklist. *Epilepsy Behav*. 2020;103(pt B):106419. doi:10.1016/j.yebeh.2019.07.020
61. Odom N, Bateman LM. Sudden unexpected death in epilepsy, periictal physiology, and the SUDEP-7 inventory. *Epilepsia*. 2018;59(10):e157–e160.
62. Barbour K, Hedorffer DC, Tian N, et al. Automated detection of sudden unexpected death in epilepsy risk factors in electronic medical records using natural language processing. *Epilepsia*. 2019;60(6):1209–1220.
63. Indiana University. Improving patient communication about SUDEP. ClinicalTrials.gov. identifier: NCT03502759. Posted April 19, 2018. Accessed August 7, 2020. https://clinicaltrials.gov/ct2/show/NCT03502759
64. Henning O, Nakken KO, Lossius MI. People with epilepsy and their relatives want more information about risks of injuries and premature death. *Epilepsy Behav*. 2018;82:6–10.
65. Ronen GM. Applying ethical principles in discussing SUDEP with patients and families. *Epilepsy Behav*. 2017;70(pt A):269–270.
66. NYU Langone Health. Risk factors for sudden unexplained death in epilepsy (SUDEP). ClinicalTrials.gov. identifier: NCT01662453. Posted August 10, 2012. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT01662453
67. University Hospital, Montpellier. Risk factors of SUDEP (PRERIES). ClinicalTrials.gov. identifier: NCT03074279. Posted March 8, 2017. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT03074279

68. Mayo Clinic. Neural circulatory control and SUDEP risk (NC-SUDEP). ClinicalTrials.gov. identifier: NCT02813980. Posted June 27, 2016. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT02813980
69. University of Iowa. Carbon dioxide (CO2) chemosensitivity and SUDEP. ClinicalTrials.gov. identifier: NCT04134754. Posted October 22, 2019. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT04134754
70. Hospices Civils de Lyon. National network for the study of predictors and prevention of sudden unexpected death in drug-resistant partial epilepsies (REPOMSE). ClinicalTrials.gov. identifier: NCT02572297. Posted October 7, 2015. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT02572297
71. Petrucci AN, Joyal KG, Purnell BS, Buchanan GF. Serotonin and sudden unexpected death in epilepsy. *Exp Neurol*. 2020;325:113145. doi:10.1016/j.expneurol.2019.113145
72. Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. SUDEP mechanisms: the pathway of prevention. *Nat Rev Neurol*. 2014;10(5):271–282.
73. Sainju RK. Abnormal ventilatory response to carbon dioxide: a potential biomarker for seizure induced respiratory depression and modification by SSRI. ClinicalTrials.gov. identifier: NCT02929667. Posted October 11, 2016. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT02929667
74. Hospices Civils de Lyon. Efficacy of naloxone in reducing postictal central respiratory dysfunction in patients with epilepsy (ENALEPSY). ClinicalTrials.gov. identifier: NCT02332447. Posted Month day, year. Accessed August 10, 2020. https://clinicaltrials.gov/ct2/show/NCT02332447
75. Patterson AL, Mudigoudar B, Fulton S, et al. SmartWatch by SmartMonitor: assessment of seizure detection efficacy for various seizure types in children, a large prospective single-center study. *Pediatr Neurol*. 2015;53(4):309–311.
76. Van Poppel K, Fulton SP, McGregor A, et al. Prospective study of the Emfit Movement Monitor. *J Child Neurol*. 2013;28(11):1434–1435.
77. Fulton S, Van Poppel K, McGregor A, et al. Prospective study of 2 bed alarms for detection of nocturnal seizures. *J Child Neurol*. 2012;28(11):1430–1433.
78. Regalia G, Onorati F, Lai M, et al. Multimodal wrist-worn devices for seizure detection and advancing research: focus on the Empatica wristbands. *Epilepsy Res*. 2019;153:79–82.
79. Hanna J, Kerr M, Sen A. Executive summary and recommendations. *Epilepsy Behav*. 2020;103(pt B):106650. doi:10.1016/j.yebeh.2019.106650