REVIEW ARTICLE



# Can We Prevent Sudden Unexpected Death in Epilepsy (SUDEP)?

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**ABSTRACT:** Sudden unexpected death in epilepsy (SUDEP) remains an important cause of epilepsy-related mortality, especially in patients with refractory epilepsy. The exact cause is not known, but postictal cardiac, respiratory, and brainstem dysfunctions are implicated. SUDEP prevention remains a big challenge. Except for low-quality evidence of preventive effect of nocturnal supervision for SUDEP, no other evidence-based preventive modality is available. Other potential preventive strategies for SUDEP include reducing the occurrence of generalized tonic–clonic seizures using seizure detection devices, detecting cardiorespiratory distress through respiratory and heart rate monitoring devices, preventing airway obstruction (safety pillows), and reducing central hypoventilation using selective serotonin reuptake inhibitors and adenosine and opiate antagonists. However, none of the above-mentioned modalities has been proven to prevent SUDEP. The present review intends to provide insight into the available SUDEP prevention modalities.

**RÉSUMÉ : La mort subite imprévisible liée à l'épilepsie (MSIE) : accident évitable?** La mort subite imprévisible liée à l'épilepsie (MSIE) est une cause importante de mortalité, surtout dans les cas de maladie réfractaire. On ne connaît pas la cause exacte, mais la survenue de troubles cardiaques, respiratoires et du tronc cérébral post-crise est incriminée, et la prévention de la MSIE pose un sérieux défi. Aucune donnée probante sur des mesures de prévention de la MSIE n'a été relevée, si ce n'est des données de piètre qualité sur l'effet préventif de la surveillance nocturne. Certes, il existe plusieurs autres mesures potentielles de prévention de la MSIE, dont la diminution du nombre de crises tonico-cloniques généralisées, des dispositifs de détection des crises d'épilepsie, des dispositifs de détection de détresse cardiorespiratoire par des dispositifs de surveillance de la fréquence respiratoire et de la fréquence cardiaque, la prévention de l'obstruction des voies respiratoires (oreillers anti-étouffement), la diminution de l'hypoventilation d'origine centrale par des inhibiteurs spécifiques du recaptage de la sérotonine (ISRS), des inhibiteurs de l'adénosine et des antagonistes des opiacés, mais aucune d'entre elles ne s'est montrée efficace dans la prévention de la MSIE. Aussi la synthèse ici présentée vise-t-elle à faire état de différentes mesures de prévention de la MSIE.

**Keywords:** Epilepsy, Sudden unexpected death in epilepsy (SUDEP), Prevention, SSRIs, Nocturnal supervision

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## Introduction

Sudden unexpected death in epilepsy (SUDEP) is an important direct epilepsy-related cause of death in people with epilepsy. The incidence of sudden death is 20 times higher in patients with epilepsy compared to the general population.[1] The incidence of SUDEP in adults is 1.2 (0.64–2.32) per 1000 patient-years. The incidence of SUDEP in children has been reported to vary between 0.22 and 1.17 per 1000 patient-years in various studies, with a higher incidence in children with refractory epilepsy (3.8/1000).[2–5] In a recent publication on the North American SUDEP registry, 27% of the 237 patients with SUDEP were reported to be less than 16 years of age.[6] The authors also noted the presence of SUDEP in 7 (3%) cases with well-controlled epilepsy. Thus, the risk of developing SUDEP is not limited to patients with frequent or uncontrolled generalized tonic–clonic seizure (GTCS).[6]

The exact pathophysiological mechanisms are not known, but postictal-disturbed cardiac or respiratory physiology is postulated to lead to death. Both prediction and prevention of SUDEP still remain a big challenge. Till date, the proposed SUDEP preventive strategies include effective epilepsy control (medical or surgical), evaluating and managing ictal or postictal cardiorespiratory distress, nocturnal supervision, and drugs such as selective serotonergic reuptake inhibitors, and opiate and adenosine antagonists which may help to prevent central apnea.[7]

In a recent Cochrane review, except for low-quality evidence of preventive effect of nocturnal supervision for SUDEP, no evidence was found for the effectiveness of seizure detection devices, safety pillows, early surgical evaluation, serotonin reuptake inhibitors (SSRIs), educational programs, and opiate and adenosine antagonists in preventing SUDEP in patients with epilepsy.[8]

Conducting randomized controlled trials for evaluating modalities to prevent SUDEP is not feasible; hence, alternative surrogate endpoints such as emergency room attendance, injuries, post-seizure apnea, and heart rate variability (HRV) have been used.[9,10] Population-based interventions in communities with SUDEP registries may be needed to establish the role of SUDEP preventive interventions.

SUDEP counseling of adult patients and parents of children with epilepsy is recommended,[11] but unless preventive strategies are explained, such counseling may lead to panic and anxiety

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among caregivers and patients. The present review intends to provide an insight into the potential ways of SUDEP prevention.

## Identifying Patients at Risk

The MORTEMUS study highlighted the role of centrally mediated postictal respiratory and cardiac compromise as a key mechanism leading to SUDEP.[12] Intrinsic brain mechanisms leading to or associated with seizure termination have been postulated to lead to a centrally mediated neurovegetative breakdown and postictal generalized electroencephalogram (EEG) suppression.[7,12] Animal studies have implicated postictal dysfunction of brainstem structures which control autonomic functions, which can lead to sudden cardiorespiratory arrest in SUDEP.[13–15]

The first crucial step toward SUDEP prevention is to correctly identify the subgroup of people with epilepsy who are at high risk for developing SUDEP. This can be done by evaluating the patient using safety checklists, inventories such as SUDEP-7 inventory, and genetic testing, and by studying specific EEG changes which have been associated with SUDEP.[7,16,17]

### Checklist and Inventory

Past studies have highlighted the possible role of 17 factors associated with increased risk of SUDEP, some of which are potentially modifiable. These form the background of the seizure and SUDEP safety checklist. This is a 10-minute risk assessment tool which can be used in daily practice in epilepsy clinics for screening patients who are at high risk of developing SUDEP. These checklists are also available on mobile applications.[18–20] However, no critical analysis of checklists and inventories is available till date.

These factors include sleeping in prone position, unclear treatment history, primary generalized epilepsy, increasing seizure frequency, compliance issues, alcohol problem, subtherapeutic antiepileptic drug (AED) levels, lack of night surveillance, duration >15 years, early-onset epilepsy, frequent AED changes, use of anxiolytic medication, intellectual disability (ID), male gender, patients on antidepressants and on carbamazepine, and increasing seizure severity.[18–20]

Of the 17 risk factors, 7 are potentially modifiable. These are unclear treatment history, poor adherence to medication, subtherapeutic medication levels, alcohol misuse, no night surveillance, sleeping in the prone position, and increasing seizure frequency ($p < 0.001$). Non-modifiable risk factors included duration of epilepsy and the presence of GTCSs.[21]

In a study on the association between SUDEP-7 inventory and HRV, the SUDEP-7 score was found to be inversely and significantly associated with HRV. The results suggest that older age, longer duration of epilepsy, and the presence of ID may increase the risk of SUDEP through their direct influence on decreasing the vagus nerve-mediated HRV.[22,23]

### Genetic Factors

Understanding the genetic basis for SUDEP is important in identifying patients and family members at risk. In a recent study, an exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes was performed in 61 patients with SUDEP.[24] De novo mutations were identified in 28/61 cases (46%). Four patients (7%) had mutations in common genes responsible for long QT syndrome, 9 (15%) had candidate pathogenic variants in dominant cardiac arrhythmia genes, and 15 (25%) had mutations or candidate pathogenic variants in dominant epilepsy genes. No gene reached genome-wide significance with rare variant collapsing analysis. *DEPDC5* ($p = 0.00015$) and *KCNH2* ($p = 0.0037$) were among the top 30 genes identified.[24]

### EEG Markers

Postictal generalized EEG suppression (PGES) is the term used for diffuse EEG "flattening" after seizure cessation. It is defined as postictal unilateral or bilateral EEG suppression of >1-second duration occurring immediately or within 30 seconds of seizure cessation with an amplitude of <10 mV.[25] PGES is usually seen after GTCS. In a retrospective study of 48 epilepsy cases, 27% (13) of those who had GTCS had PGES followed by postictal slowing.[26] The reported occurrence of PGES after convulsive seizures is 40%–60% in patients with generalized convulsive seizures as compared to 1%–2% in cases with focal seizures.[25,27]

In some SUDEP patients, EEG recordings after terminal seizures had demonstrated PGES.[3,7] These findings have initiated the debate over its potential role as a predictor of future SUDEP risk and also in the pathophysiology of SUDEP, wherein the initiating event is considered as "electrocerebral shutdown."

Longer duration (> 50 seconds) PGES are associated with increased risk of SUDEP.[22,27] Children with PGES had higher SUDEP-7 scores than children without PGES.[25] Increased risk of PGES in children has been noted in sleep, with shorter duration of clonic phase, symmetric tonic extension posturing, and terminal burst suppression after seizure.[3]

## Effective Epilepsy Treatment

An important measure for SUDEP prevention is effective epilepsy treatment and seizure control.[7] This can be achieved using appropriate AED, timely presurgical referral in drug refractory cases, and surgery in candidates meeting the surgical criteria.

A meta-analysis (2011) of adult patients with refractory epilepsy reported that patients receiving an add-on AED had a sevenfold lower risk of SUDEP (0.9/1000 vs. 6.9/1000 patient-years) as compared to patients receiving an add-on placebo.[28]

Another important step is patient education regarding drug compliance and adherence, lifestyle modification to avoid seizure-triggering factors such as sleep deprivation, stress, and excess alcohol intake, and educating them about care plans for seizure clusters (rescue medicine) and home management of seizures. Appropriate advice regarding AED use during gastrointestinal illness, intercurrent illness, concomitant use of other drugs, use of oral contraceptive pills, and pregnancy should be given.

Surgical removal of epileptogenic zone is effective seizure control treatment, but its role in SUDEP prevention is debatable. Studies have reported that failed surgical candidates have higher risk of SUDEP.[29–31] But there is no strong evidence to support this. It is likely that patients failing temporal lobe surgery may have their epileptogenic zone involving extratemporal brain regions which control cardiorespiratory functions, leading to



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increased risk of SUDEP post-surgery.[32–34] Hence, delineation of the epileptogenic zone and appropriate surgical management is of paramount importance..

### Detect Seizures and Cardiorespiratory Distress

As SUDEP is known to follow a seizure, seizure detection and effective termination may help to prevent the postictal cardiorespiratory compromise and thus prevent SUDEP. This can be achieved by the following measures:

#### Nocturnal Supervision

Past studies have highlighted the role of nocturnal supervision for detecting seizures and reported it to be protective.[7,35,36] Combined use of nocturnal supervision with seizure detection devices may enable more effective seizure detection, but evidence to prevent SUDEP is lacking.

Disadvantages of nocturnal supervision include high false-positive or negative detection rates, effect on quality of life issues, and cultural acceptance. In addition, one must also be aware of the fact that the intervention by a witness does not necessarily preclude the occurrence of SUDEP. Though turning the patient from prone to recovery position after GTCS may reverse respiratory compromise, more effective resuscitation may be needed.

#### Seizure Detection Devices

A variety of seizure detection devices are currently available. Though these may be effective in detecting seizures, some are marketed as being helpful to prevent SUDEP though the evidence for the same is lacking. Use of these devices should be individualized according to patient preference, seizure profile (nocturnal, generalized, and frequency), and overall risk of SUDEP. More extensive clinical investigation and trials are needed to find out their appropriate role in the SUDEP prevention algorithm.[7]

#### Prone Position and SUDEP

SUDEP cases are more often found prone, but extrapolating this observation to sleeping prone as a contributing factor has no supportive evidence. A recent systematic review and meta-analysis of 253 cases of SUDEP reported that approximately 73.3% of patients were found in prone position (95% confidence interval [CI] 5 65.7%, 80.9%, $p < 0.001$). Prone position was observed in 85.7% (95% CI 5 74.6%, 93.3%) of patients aged < 40 years of age (95% CI 5 74.6%, 93.3%). The likely possible mechanism suggested is that turning to prone position during GTCS followed by postictal apnea (commonly associated with PGES) leads to obstructive apnea. In addition, prone position is associated with impaired arousal.[37] However, as the prone positioning occurs during the seizure, a "back-to-sleep campaign," such as that for SIDS prevention, may not be very helpful. Most experts believe that individuals with epilepsy turn in their sleep or turn with a GTCS making the bedtime sleep position irrelevant.

For SUDEP prevention, if the seizure is witnessed, turning patient from prone to lateral recovery position and stimulating the patient may help.

### Prevent Airway Obstruction

#### Safety Pillows

Latex safety pillows (ventilated foam pillows) may reduce the contribution of prone position toward postictal cardiorespiratory distress and prevent obstructive apnea.[7,38] However, no studies are available to support their role in SUDEP prevention.

### Reduce Central Hypoventilation

#### Serotonergic Drugs – SSRI

Lower brainstem serotoninergic nuclei play an important role in the regulation of respiration. Serotonin neurons in the brainstem sense rising carbon dioxide and low pH, thereby stimulating breathing and arousal.[39] Abnormalities of serotonergic neurons have been previously reported in SIDS and in a mouse model of SUDEP, thereby highlighting possible role of selective serotonin receptor inhibitors (SSRIs) for SUDEP prevention.[7,40–42] Use of SSRIs may decrease the risk of potential apnea.

In animal studies, fluoxetine has been shown to prevent the occurrence of fatal seizure-induced apnea in SUDEP.[41–44]. In a retrospective study, it was seen that postictal hypoxemia was significantly less frequent in patients with drug refractory partial epilepsy receiving SSRIs as compared to those who were not on SSRIs.[45]

Two double-blind, randomized, placebo-controlled trials (NCT02569970, NCT02929667) are underway (results awaited) to assess the efficacy of Fluoxetine against seizure-induced central apnea.

#### Reduce Adenosine and Endogenous Opioid-Induced Brainstem Depression

##### *Inhibitors of Opiate and Adenosine Receptors*

Seizure activity induces massive release of endogenous opioids and adenosine which helps in seizure termination. But their excessive release can lead to postictal apnea. The opioid antagonist naloxone may potentially reduce the occurrence of postictal apnea. A randomized control trial, ENALEPSY (NCT02332447) study, on postictal naloxone is presently underway (recruitment completed and results awaited) to assess the efficacy of naloxone in reducing the severity of the postictal central respiratory dysfunction after GTCS.

Animal studies have reported that treatment with caffeine may directly prevent apnea and cardiopulmonary suppression by blocking $A_1$Rs as well as $A_{2A}$Rs in brainstem, thus preventing SUDEP.[41] A recent study has shown improved survival in mice model from $23.75 \pm 1.35$ minutes to $54.86 \pm 6.59$ minutes ($p < 0.01$) when caffeine is given 5 minutes after the seizure onset.[46] However, caffeine has proconvulsant effect and can aggravate the duration, frequency, or severity of seizures and is not recommended.[47]

### Cardiac and Diaphragmatic Pacing

Cardiac and diaphragmatic pacing are potential SUDEP prevention modalities which need to be explored. Standard cardiac pacing prevents brain hypoperfusion but may not reverse respiratory failure which might require diaphragmatic pacing or phrenic nerve stimulation.



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***Potential modalities for prevention of SUDEP***

- Identify patients at risk – GTCS, uncontrolled epilepsy, co-morbid developmental delay/ID (SUDEP checklists).
- Discussion with families
- Early surgical referral
- Appropriate AED therapy, stress on compliance
- Lifestyle factors – avoiding sleep deprivation, stress, alcohol
- AED advice during intercurrent illnesses such as GI, concurrent drug, and OCP intake
- Train caregivers in home management of seizures
- Nocturnal supervision (if culturally acceptable)
- Safety pillows
- Intranasal midazolam, turning from prone to recovery position and stimulating the patient
- BLS training to willing caregivers of high-risk patients
- Seizure monitoring devices may be discussed with emphasis that we do not have evidence of SUDEP prevention.

***Figure 1:*** *Potential Modalities for Prevention of SUDEP.*

## Preventing SUDEP in the Epilepsy Monitoring Unit (EMU)

SUDEP and near-SUDEP have been reported from EMUs.[12,48] Special attention should be given to all patients admitted to the EMU for elective VEEG monitoring. Apart from providing basic care, systematic monitoring for ictal/postictal cardiorespiratory compromise is a crucial part of their management.

Systematic monitoring using electrocardiography and SpO2 devices with appropriate alarms should be done. EMU should have organization of emergency codes. The staff should be trained to quickly identify ictal/postictal cardiorespiratory distress and start resuscitation whenever needed. Animal studies have highlighted the role of postictal oxygen therapy for SUDEP prevention.[49] Oxygen should be started in patients with postictal respiratory distress or decreased oxygen saturation. Precautions should be taken, while tapering the AEDs as rapid withdrawal may induce seizures. Many patients undergoing epilepsy surgery workup have their AED tapered while admitted to the EMU. In a recent study of 25 patients with SUDEP (11 monitored, 5 non-monitored, and 9 near-SUDEP), in 9 (36%) patients AEDs were reduced by more than 50% and in 5 (20%) patients AEDs were completely withdrawn. This suggests a possible role of rapid withdrawal in promoting the terminal seizure and associated cardiorespiratory arrest.[15]

## Conclusion

SUDEP remains a significant cause of epilepsy-associated mortality in adult and children patient population and its prevention remains a big challenge. Identifying patients at risk, attaining good seizure control using appropriate AED and early surgical referral along with training caregivers in home management of seizures, and detecting seizures and cardiorespiratory arrest are potential ways of reducing SUDEP-related mortality (Figure 1).

Advent of seizure detection devices, safety pillows, drugs reducing adenosine and endogenous opioid-induced brainstem depression, and cardiac and phrenic pacing have paved the way for future prevention modalities, but more studies are needed to establish their effectiveness.

## Conflict of Interests

None.

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