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Risks and predictive biomarkers of SUDEP

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Abstract

- Purpose of review: This review updates our knowledge regarding SUDEP risks, risk factors, and investigations of putative biomarkers based on suspected mechanisms of SUDEP.

- Recent findings: The overall incidence of SUDEP in adults with epilepsy is 1.2/1000 patient-years, with surprisingly comparable figures in children in recently published population-based studies. This risk was found to decrease over time in several cohorts at a rate of –7% per year, for unknown reasons. Well-established risk factors include frequency of generalized tonic-clonic seizures, while adding antiepileptic treatment, nocturnal supervision and use of nocturnal listening device appear to be protective. In contrast, recent data failed to demonstrate the predictive value of heart rate variability, periictal cardiorespiratory dysfunction, and postictal generalized EEG suppression. Preliminary findings suggest that brainstem and thalamic atrophy may be associated with a higher risk of SUDEP. Novel experimental and human data support the primary role of GTCS-triggered respiratory dysfunction and the likely contribution of altered brainstem serotonergic neurotransmission, in SUDEP pathophysiology.

- Summary: While significant progress has been made during the past year in the understanding of SUDEP mechanisms and investigation of numerous potential biomarkers, we are still missing reliable predictors of SUDEP beyond the well-established clinical risk factors.

Keywords

Epilepsy; SUDEP; biomarker; risk; predictor

Introduction

In 2017, the American Academy of Neurology (AAN) published guidelines on the incidence and risk factors of Sudden Unexpected Death in Epilepsy Patient (SUDEP). Based on the

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analysis of 12 Class I studies, the risk of definite/probable SUDEP was estimated at 1.2/1000 patient-years (PY) in adults and at 0.22/1000 in children.¹ However, this latter figure has since been challenged by two population-based studies reporting similar SUDEP rates of 1.11/1000 PY in children, thus comparable to those found in adults.^{2,3} While SUDEP in childhood has been primarily reported in the most severe forms of epilepsy, in particular those related to gene mutations such as in Dravet syndrome (DS) where it reached 6/1000 PY, it was recently reported in three children suffering from benign epilepsy with centrotemporal spikes (BECTS).⁴ Beside DS, genetic epilepsies related to mutation of GATOR1 complex genes (DEPDC5, NPRL2, NPRL3) also appear to carry a high risk of SUDEP, affecting 10% of 73 families.⁵

In the Swedish population-based study cited above, the authors observed a decrease in SUDEP incidence which averaged 7% per year during 6-year follow-up.⁶ A similar observation was made in a retrospective analysis of 40,443 patients treated with vagus nerve stimulation (VNS) for an average duration of 7.6 years.⁷ There was a significant decrease in age-adjusted SUDEP rate from 2.47 to 1.68/1000 PY between years 1–2 and 3–10 ($p = 0.002$).⁷ A large reduction in SUDEP risk from 6.8/1000PY to 1.7/1000 PY was also reported in a tertiary epilepsy center between time periods 1981–1992 and 1999–2010.⁸ Interestingly, all three studies, while using completely different methodologies, provide figures compatible with a 7% annual decrease in SUDEP rate. While reasons for these observations are unclear, some have hypothesized the role of better supervision in tertiary epilepsy centers.⁸

The epidemiological figures reported above pooled data from populations which risk of SUDEP varies by almost a factor of 100,⁹ with highest incidence in patients awaiting or having failed epilepsy surgery (9.3/1000 PY).¹⁰ Extrapolation from population-based and case-control studies suggest that patients with frequent GTCS may suffer even higher risk, up to 18/1000 PY.¹¹ This heterogeneity stresses the need for reliable predictors and biomarkers of SUDEP to appropriately inform and manage patients with epilepsy and their families.

SUDEP risk factors identified in case-control studies

The AAN SUDEP guidelines have identified six risks factors.¹ The greatest odd ratio (OR) was found for GTCS frequency >3/year (OR=15.46). The sole presence of GTCS was associated with an OR=10.¹ This was followed by the lack of adding an AED in drug resistant patients (OR=6), and the lack of terminal seizure freedom during the last 1–5 years (OR=4.7).¹ Two factors were considered to reduce the risk of SUDEP, nocturnal supervision (OR=0.4) and use of nocturnal listening device (OR=0.1).¹ Other previously reported risk factors were considered to be associated with conflicting or too low level of evidence (see table 1).¹

More recent studies have essentially confirmed the above findings. A retrospective case-control study of 41 SUDEP patients specifically investigated the frequency of GTCS during the 3 months preceding death, and found this frequency to be significantly higher in SUDEP cases than in controls.¹² They also observe an increase in the frequency of GTCS during the

last 3 months before SUDEP.¹² As we previously hypothesized,¹³ these data suggest that the individual risk of SUDEP may vary overtime, and increase as a function of GTCS frequency. Another retrospective case-control study of 60 SUDEP cases in residential care settings found that both the presence and frequency of nocturnal GTCS were associated with higher risk of SUDEP.¹⁴ When comparing SUDEP incidence between the two centers which used different level of supervision, that with the lowest grade of supervision had significantly higher SUDEP rate (6.12/1000 PY) than the other (2.21/1000 patient-years).¹⁴ In the Swedish population-based study, women with epilepsy had a 5-fold higher rate of SUDEP if suffering from a psychiatric comorbidity.³

A retrospective case-control study of 16 SUDEP and 48 controls specifically tested the predictive value of the revised SUDEP-7 inventory.¹⁵ The latter was developed as a surrogate marker of the overall SUDEP risk, based on the presence or absence of several previously reported risk factors.¹⁶ The authors failed to observe a significant difference in the revised SUDEP-7 inventory score between SUDEP cases and controls.¹⁵ While this negative finding may partly reflect the small sample size of the study, it also points to the limitation of validating any new SUDEP risk factor against surrogate markers such as the revised SUDEP-7 inventory.

The same study also failed to find association between SUDEP and interictal heart rate variability (HRV) and periictal cardiorespiratory dysfunction.¹⁵ In contrast, a retrospective HRV study of 80 patients with drug-resistant seizures including 40 with a sodium-channel gene mutation, 10 of whom later died of a SUDEP, found more severe autonomic dysregulation in SUDEP patients.¹⁷ These patients suffered reduced HRV during wakefulness and either extremely high or extremely low ratios of sleep-to-awake HRV.¹⁷

Postictal generalized EEG suppression (PGES) was originally proposed as a strong predictor of SUDEP based on a case-control study of 10 SUDEP patients.¹⁸ However, this finding was not reproduced in a consecutive study of 19 SUDEP.¹⁹ More recently, a third study of 16 SUDEP cases also failed to demonstrate an association between SUDEP and PGES.¹⁵ A fourth series of 17 SUDEP cases even found opposite results with controls exhibiting more frequent post-GTCS PGES (47%) than SUDEP patients (32%), more frequent PGES >50 seconds, and significantly longer mean duration of PGES (49 versus 24 s, $p=0.0002$).²⁰ Several reasons are likely to explain such level of discrepancies between studies, including their small sample size, their retrospective design, and the inherent difficulties in adjudicating PGES.²¹ Hopefully, this latter issue is being tackled by the development of automated EEG suppression detection tool.²¹ Such tool would benefit from a better understanding of the intracerebral EEG patterns underlying scalp-EEG detected PGES, which proved to cover a wide range of focal to generalized postictal EEG suppression patterns.²² Another interesting line of research is the use of computational model of seizure and PGES.²³ Using this approach, the authors demonstrate a significant link between terminal interclonic interval and duration of PGES.²³ Overall, while PGES remains of unclear value for predicting SUDEP, recent methodological developments justify the continued investigation of this biomarker.

MRI volumetric studies have revealed abnormalities in SUDEP patients as compared to controls. In a study of 12 SUDEP patients, 34 epilepsy patients at high risk of SUDEP, 19 at low risk, and 15 healthy controls, the SUDEP and high-risk groups showed increased volume of the right anterior mesial temporal region and decreased volume of the pulvinar as compared to controls.²⁴ Another study of two SUDEP patients reported greater atrophy of the dorsal mesencephalon as compared to a group of temporal lobe epilepsy patients.²⁵ More recently, MRI from 26 SUDEP patients showed that volume loss in the raphe/medulla oblongata at the obex level correlated with the time to SUDEP.²⁶ While the above group studies are encouraging, moving towards MRI biomarkers that would help predicting the risk of SUDEP at the individual level remains a challenge.

From SUDEP mechanisms to novel biomarkers

Search for novel SUDEP biomarkers is likely to be more successful if based on a better understanding of the mechanisms leading to SUDEP. The MORTEMUS study has originally shown that all SUDEP captured during video-EEG recordings displayed a similar pattern, starting with a secondarily GTCS, followed by a short period characterized by tachypnea and tachycardia, then a disruption of both respiratory and cardiac activity leading to terminal cardiorespiratory arrest.²⁷ Apnea always occurred within 3 minutes postictal and prior to asystole, suggesting that respiratory disorders play a major role in driving the sequence of autonomic abnormalities.²⁷ A number of clinical and experimental data have since confirmed these hypotheses, as well as the lack of appropriate arousal, all of which are likely to reflect postictal brainstem dysfunction.²⁸ Even in Dravet syndrome, where the presence of mutated sodium channel gene SCN1A has suggested a potential cardiac origin of SUDEP, recent data point to the primary role of respiratory dysfunction.²⁹ Accordingly, DS mice model harboring a *Scn1a*R1407X/+ loss-of-function mutation suffer spontaneous and heat-induced fatal central apnea.²⁹ However, whether postictal respiratory disorders leading to SUDEP are primarily central or obstructive, remains uncertain. Evidence gathered in animal models and patients, including revisited MORTEMUS data, suggest the possible role of perictal laryngospasm.^{30–33} Recent experimental data suggest that fatal laryngospasm might result from reflux of stomach acid into the larynx.³⁴ In any event, all above findings encourage the development of SUDEP biomarkers probing peri-ictal respiratory disorders.

Circumstances of SUDEP outside the epilepsy monitoring unit (EMU) also offer insights into the mechanisms of SUDEP. A Swedish cohort of 329 SUDEP has allowed to revisit this issue, showing that 91% of cases died at home, 83% unobserved, 65% in bed (70% in the prone position) and 58% at night.³⁵ These data confirm, in a much larger series than those previously available, the typical circumstances of SUDEP.²⁷ Accordingly, biomarkers informing on the characteristics of nocturnal seizures and their consequences on cardiorespiratory functions might be of value. While the majority of SUDEP patients are found prone in their bed, a perictal prone position appears to be rare event in video-EEG recorded GTCS (<5%).^{36,37} When present, it reflects the fact that the patient was sleeping prone in two-third of cases, whereas he turned prone during seizure in the remaining cases.³⁶ This is in contrast with the fatal GTCS recorded in the MORTEMUS study, where most patients turned prone during seizure.³⁸

Novel insights into the pathophysiology of SUDEP were recently provided by the investigation of the brainstem from 14 patients who died of a SUDEP, compared to the pathological material from six epilepsy controls, seven DS patients, and 13 non-epilepsy controls.³⁹ SUDEP patients demonstrated reduction of labeling for somatostatin, galanin, tryptophan hydroxylase and neurokinin 1 receptors in the ventrolateral medulla, as compared to controls.³⁹ Serotonin transporter labeling was also reduced in the raphe, and its co-localization with tryptophan hydroxylase reduced in the ventrolateral medulla.³⁹ These data further support the view that brainstem serotonergic abnormalities promote SUDEP,⁴⁰ as suggested by various experimental models, including DBA/1 mice. In the latter, most recent optogenetic study using selective stimulation of dorsal raphe serotonergic neurons could prevent the tonic component and respiratory arrest and death triggered by audiogenic seizure while other ictal features were unchanged.⁴¹

Another immunohistochemistry study of 28 SUDEP patients compared to 12 epilepsy controls and 18 nonepileptic sudden death fail to observe any difference between groups in the expression of markers for inflammation, brain blood barrier leakage, and hypoxia-inducible factor-1 α .⁴²

One study investigated whole-exome sequences (WES) on brain tissue obtained at epilepsy surgery from eight patients who later died from SUDEP and seven living controls matched for age at surgery, sex, and lobe of resection.⁴³ SUDEP patients, but not controls, displayed variants in genes involved in μ -opioid, gamma-aminobutyric acid and glutamate neurotransmission, as well as in genes associated with cardiac arrhythmia.⁴³

While the majority of SUDEP are triggered by a GTCS, other less frequent mechanisms are also at stake. Three adult patients were reported to suffer a SUDEP in EMU without evidence of a prior seizure on video-EEG recording.⁴⁴ A 20-month old patient, with a chromosomal defect, also failed to demonstrate any seizure activity at a time of SUDEP, two days after de-novo febrile status epilepticus.⁴⁵ In four SUDEP patients treated with brain-responsive neurostimulation, electrocorticogram failed to show an ictal pattern prior to death in three of them.⁴⁶ Finally, a near-SUDEP without a prior seizure was recorded in a child with focal cortical dysplasia type IIb and refractory epilepsy undergoing invasive EEG monitoring. The event was primarily characterized by diffuse EEG slowing and attenuation with apnea, followed by bradycardia.⁴⁷

Among the mechanisms that lead to non-typical seizure-triggered SUDEP, a fatal cerebral edema was reported in a 21-year-old DS patient, three hours after a single seizure.⁴⁸ Sodium channel dysfunction may have contributed to an excessive delayed postictal brain swelling.⁴⁸ Two infants harboring a SCN1A mutation were also reported to die suddenly, without any history of seizure.⁴⁹

Tentative future SUDEP biomarkers

Based on our current understanding of SUDEP mechanisms summarized in the previous section, a number of potential biomarkers have been investigated in living patients with epilepsy. However, none of these studies directly tested their predictive value of the risk of

SUDEP. Rather, they were either descriptive or looked at associations between biomarkers, including the SUDEP-7 inventory score which relevance has been challenged as previously discussed.¹⁵

Respiratory biomarkers

In a multicentric prospective series, inductance plethysmography and capillary oxygen saturation (SpO₂) were investigated during video-EEG to quantify the incidence of ictal central apnea (ICA).⁵⁰ ICA was observed in 36.5% of 312 focal seizures, and was significantly more frequent in temporal than extra-temporal lobe epilepsies ($p=0.001$).⁵⁰ The same consortium investigated ICA and postictal central apnea in 148 GTCS.⁵¹ ICA was observed during the focal phase of seizures, prior to GTCS, in 40.4% of cases, while postictal central apnea occurred in 22.1%. The origin of ICA was investigated in two other series by performing cortical electrical stimulation during intracerebral EEG investigation.^{52,53} In both studies, stimulation of the amygdala proved to elicit central apnea, primarily during the expiratory phase.⁵³ Interestingly, apnea could be prevented by asking the patient to inhale or to breath through the mouth.^{52,53}

Looking specifically at SpO₂ during video-EEG, a series of 107 GTCS reported hypoxemia (SPO₂<90%) in 86% of seizures.⁵⁴ The occurrence of hypoxemia during the focal phase preceding GTCS was associated with lower SPO₂ nadir following GTCS. Furthermore, temporal lobe epilepsy was associated with longer time to SPO₂ recovery as compared to extra-temporal lobe epilepsy.⁵⁴ Both findings are consistent with the ICA data reported above.^{50,51} Interestingly, administration of oxygen was associated with lower rate of severe hypoxemia <70% ($p=0.046$), less severe hypoxemia ($p=0.003$) and more rapid SpO₂ recovery ($p=0.004$).⁵⁴ In one study of 48 seizures in 20 patients, sleep was found to have a significant impact on seizure-associated changes in SPO₂ by intensifying both ictal and postictal desaturation as compared to those observed during wakefulness.⁵⁵ However, another series of 165 seizures in 67 patients failed to reproduce this finding.⁵⁶

Sleep-disordered breathing (SBD) in patients with epilepsy, and its relation with the revised SUDEP-7 inventory, were investigated in two series.^{57,58} In the first study, an obstructive apnea syndrome was diagnosed in 35% of the 49 patients and was associated with high score (5) at the revised SUDEP-7 inventory.⁵⁷ The second study investigated SBD together with periictal cardiorespiratory dysfunction and sex-steroid hormones.⁵⁸ SBD was observed in 88% of cases, but did not correlate with the other biomarkers, including the revised SUDEP-7 inventory score.⁵⁸

Serotonin biomarkers

The serotonergic system is known to play a major role in the physiology of brainstem respiratory centers, and suspected to be altered in SUDEP.³⁹ Postictal serotonin (5-HT) blood levels were investigated in 41 patients with focal or generalized seizures.⁵⁹ As compared to interictal values, postictal 5-HT blood levels significantly increased following GTCS ($p=0.002$), while remaining unchanged after focal seizures without generalization.⁵⁹ Interestingly, the shorter the duration of the tonic phase, the greater the rise in post-GTCS 5-HT.⁵⁹ Furthermore, interictal 5-HT level correlated with duration of PGES.⁵⁹ However, one

needs to remain cautious in the interpretation of these findings given the lack of permeability of the BBB to 5-HT.

Cardiac biomarkers

Reduced heart rate variability (HRV) is a strong predictor of sudden death in patients with heart disease. HRV is also typically decreased in patients with epilepsy, in particular in those with temporal lobe or drug-resistant seizures.⁶⁰ However, we still lack evidence that this biomarker predicts the risk of SUDEP,^{15,60} except maybe for patients with sodium-channel mutation.¹⁷ In a recent series of 47 patients with drug-resistant epilepsy compared to 45 healthy controls, decreased HRV was confirmed in patients with epilepsy but failed to correlate with the SUDEP-7 inventory score.⁶¹ In an attempt to delineate more informative heart rate measures than traditional HRV, one study investigated the interictal deceleration and acceleration capacities of heart rate as well as their 24-h dynamics, in 39 patients with drug-resistant epilepsy and 33 healthy controls. Patients showed abnormal values for all parameters, suggesting inhibition of vagal modulation of heart rate. Abnormalities were greater for deceleration capacity, peaked at night between 3 and 5 A.M. and proved more discriminant than standard HRV.⁶² Ictal HRV was investigated in 13 patients with temporal lobe epilepsy undergoing intracranial EEG recording, showing greater abnormalities and autonomic imbalance towards sympathetic predominance when both temporal lobes were seizing as compared to unilateral seizure.⁶³

Heart rate function in patients with epilepsy was also studied during treadmill test. As compared to controls, patients demonstrated lower peak heart rate, duration of exercise, Duke Score, and metabolic equivalent of task.⁶⁴ Patients also suffered from more frequent chronotropic incompetence.⁶⁴

While ictal asystole (IA) appears to be a self-terminating event,⁶⁵ it is yet unknown whether history of periictal bradycardia, asystole or nonsustained ventricular tachycardia increase the risk of SUDEP. In a study of 182 GTCS in 69 patients, 10 seizures (5%) in 10 patients (14%) triggered one such potentially high-risk cardiac arrhythmia.⁶⁶ These seizures were associated with longer hypoxemia than those without peri-ictal arrhythmia.⁶⁶

Early repolarization (ER), a possible biomarker of sudden cardiac death, was investigated in 354 patients with epilepsy.⁶⁷ The presence of abnormal J-wave amplitude in inferior ECG leads was significantly more frequent in epilepsy patients (19.8%) than in age-matched healthy controls (8.6%; $P = 0.002$).⁶⁷ An horizontal or descending ST segment was also more frequent in patients with epilepsy ($P < 0.001$).⁶⁷

Abnormal regulation of blood pressure during seizures could also contribute to SUDEP.⁶⁸ Two recent studies have investigated the baroreflex sensitivity (BRS) in patients with epilepsy.^{69,70} The first study investigated 14 focal seizures and nine GTCS. While BRS increased following 86% focal seizures, it significantly decreased in 89% of GTCS, suggesting a transient alteration of cardiovascular homeostatic control.⁷⁰ Another study explored BRS in 19 focal seizures and 7 GTCS and confirmed these findings with a major BRS drop following GTCS (from 15 to 3.1 ms/mm Hg) but not after focal seizures.⁶⁹ Intracerebral electrical stimulation performed in 12 patients undergoing invasive EEG

recordings showed that stimulation of Broadman area 25 was selectively associated with striking systolic hypotensive changes.⁷¹

Cardiac pathology may also prove of interest, given the frequent observation of myocyte hypertrophy and myocardial fibrosis in SUDEP patients.⁷² Cardiac echocardiographic biomarkers associated with the risk of sudden death in the general population were investigated in 30 patients with temporal lobe epilepsy and no history of cardiovascular diseases.⁷³ As compared to controls, epilepsy patients showed significantly higher left ventricle stiffness and pressures, left atrial volume, and an increased prevalence of at least one of sudden death echocardiographic biomarkers.⁷³ However, another study comparing cardiac pathology between 25 SUDEP cases, 285 sudden arrhythmic death in non-epileptic patients and 104 trauma deaths revealed that SUDEP cases had similar cardiac pathology than trauma cases, and significantly less than sudden arrhythmic death in non-epileptic patients.⁷⁴ This finding suggests that the typical cardiac pathology reported in SUDEP may not be necessarily relevant to its mechanisms.

Electrodermal activity

Electrodermal activity (EDA) measured at the wrist proved to be a reliable biomarker for detecting GTCS.⁷⁵ In a recent multicentre series, EDA exhibited a significant rise in 73% of 55 GTCS in 22 patients.⁷⁶ Peri-ictal rise in EDA also correlated with the presence of PGES.^{77,78} More recently, a patient suffered a GTCS-induced SUDEP while wearing an EDA biosensor.⁷⁹ The postictal EDA rise proved to be unusually fast and large, suggesting that EDA response associated with fatal GTCS might be greater than those commonly observed during non fatal GTCS.⁷⁹

MRI biomarkers

Combined investigation of brainstem volume and HRV in 18 patients with focal epilepsy demonstrated a correlation between excessive volume loss in the periaqueductal grey/medulla oblongata autonomic nuclei and HRV ($p < 0.001$), suggesting a direct link between epilepsy-associated changes in brainstem volume and cardiac autonomic control.²⁶

Functional connectivity using resting-state fMRI was compared between temporal lobe epilepsy patients considered at low ($N=18$) and high risk ($N=14$) of SUDEP.⁸⁰ The high-risk group differed from the low-risk one in two subnetworks; one that showed reduced connectivity between the thalamus, brainstem, anterior cingulate, putamen and amygdala, and a second that demonstrated increased connectivity between the medial/orbital frontal cortex, insula, hippocampus, amygdala, subcallosal cortex, brainstem, thalamus, caudate, and putamen.⁸⁰

Finally, one MRI study specifically compared cortical thickness between patients suffering GTCS with either PGES ($N=30$) or no PGES ($N=21$).⁸¹ In comparison with patients with no PGES, those with PGES demonstrated reduced cortical thickness in the right paracentral lobule, inferior parietal lobule, supramarginal gyrus and middle temporal lobe.⁸¹ Additional cortical thinning was observed in the right superior parietal lobule and supramarginal gyrus as compared to healthy controls.⁸¹

Conclusion

Recent studies have confirmed well-established risk factors of SUDEP, including the primary role of GTCS as well as the lack of intervention and nocturnal supervision where appropriate, all of which are fully consistent with our understanding of the mechanisms and circumstances of SUDEP. Numerous biomarkers of interictal and periictal autonomic functions and brain networks are being investigated in relation to SUDEP but still lack evidence of predicting its occurrence.

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Key bullet points:

1. The risk of SUDEP in patients with epilepsy is about 1.1 to 1.2/1000 patient-years in both children and adults.
2. The primary SUDEP risk factors are the presence and frequency of GTCS. Other well-established factors are the lack of: seizure freedom, adding an AED in refractory epilepsy, nocturnal supervision and nocturnal listening device.
3. Numerous biomarkers of interictal and periictal autonomic functions and brain networks are being investigated in relation to SUDEP but still lack evidence of predicting its occurrence.

Table 1

Summary of AAN Practice Guidelines on SUDEP risks.

<u>Recommendations of established risk factors</u>		
Factor	OR (95% CI)	level of evidence
Presence of GTCS	10 (17–14)	Moderate
> 3 GTCS per year	15 (9.9–24)	High
Not seizure-free for 1–5 y	4.7 (1.4–16)	Moderate
Not adding an AED in refractory epilepsy	6 (2–20)	Moderate
Nocturnal supervision	0.4 (0.2–8)	Moderate
Use of nocturnal listening device	0.1 (0–0.3)	Moderate
<u>No recommendation because of low evidence</u>		
Factor	Impact on SUDEP risk	
Nocturnal seizures	Increase risk	
Lamotrigine use in women	Increase risk	
Never been treated with an AED	Increase risk	
Number of AEDs used overall	Increase risk	
Extratemporal epilepsy	Increase risk	
Intellectual disability	Increase risk	
Male sex	Increase risk	
Anxiolytic drug use	Increase risk	
Any specific AED	Not a risk factor	
Heart rate variability	Not a risk factor	
<u>No recommendation: evidence is very low or conflicting</u>		
Epilepsy etiology, whether idiopathic or localization-related		
Structural lesion on MRI		
Duration of epilepsy		
Age at epilepsy onset		
Overall seizure frequency when evaluated by using all seizure types		
Medically refractory epilepsy vs no seizure in the last year		
Monotherapy vs polytherapy		
Frequent changes in AEDs		
Lamotrigine use in people with highly refractory epilepsy		
Carbamazepine, phenytoin, or sodium valproate levels		
Therapeutic drug monitoring		
Psychotropic drug use		
Mental health disorders, lung disorders, or alcohol use		
Undergoing a resective epilepsy surgical procedure		
Reduced GTCS frequency and epilepsy severity by surgery		
Engel outcome of epilepsy surgery		
Vagus nerve stimulator use for more than 2 years		
Postictal generalized EEG suppression		