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Review Article

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Risk Factors Associated with Sudden Unexpected Death in Epilepsy (Sudep): A Systematic Literature Review

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ABSTRACT

Introduction: Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality in patients with epilepsy, particularly those with refractory forms. Mechanisms involve cardiovascular autonomic dysfunction linked to generalized tonic–clonic seizures (GTCS). Despite the identification of multiple risk factors, methodological inconsistencies hinder generalization and development of effective preventive strategies.

Objectives: This review aims to identify and synthesize current evidence on risk factors associated with SUDEP, clarify discrepancies, detect knowledge gaps, and propose foundations for preventive clinical measures.

Methods: A systematic literature review was conducted in accordance with PRISMA guidelines. We included observational studies and clinical trials published in English or Spanish, retrieved from PubMed, Embase, and The Cochrane Library. Methodological quality was assessed using validated tools. Out of 348 records, 26 studies met the inclusion criteria.

Results: Recent GTCS episodes were strongly associated with higher SUDEP risk (OR = 26.81; 95% CI: 14.86–48.38). High seizure frequency and lack of night supervision increased the risk even further (OR = 67.10; 95% CI: 29.66–151.88). Poor adherence to antiepileptic treatment also emerged as a significant risk factor (OR = 2.75; 95% CI: 1.58–4.78).

Discussion: GTCS frequency and treatment adherence are critical in SUDEP risk. Implementing night monitoring and adherence-enhancing strategies may help reduce incidence. However, limitations such as heterogeneous SUDEP definitions and small sample sizes underline the need for robust, prospective research to refine prevention efforts.

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Introduction

Epilepsy is one of the most prevalent chronic neurological conditions, it has a global incidence close to 1% of the world population [1]. Despite progress in anticonvulsant and surgical therapies, patients still face an increased risk of premature death. Sudden unexpected death in epilepsy (SUDEP) is one of the leading mortality causes which is directly related to this disease, especially in refractory epilepsy patients [2]. SUDEP is defined as the sudden and unexpected death of a person who has epilepsy, which mostly occurs while sleeping [3].

Underlying mechanisms of SUDEP are complex and multifactorial, some of them are cardiac disorders, autonomic dysfunction and respiratory suppression during or after convulsive crises, mostly in generalized tonic–clonic seizures [4]. Severity and frequency of these crises, along with other factors such as prone position during the event, adherence to treatment and psychiatric or cardiovascular comorbidities have been recognized as contributing risk factors.

Even though there have been a high number of studies dedicated to SUDEP in these last decades, there are still some important limitations in the comprehension of specific risk factors. Recent studies have shown important predictors, such as nocturnal tonic-clonic seizures, use of multiple anticonvulsants and low heart rate variability (HRV) as major high risk factors [5]. However, a lack of methodological uniformity and small sample sizes used in various studies limit result generalizability [6].

In addition, more systematic analyses are needed to integrate factors such as cardiac and respiratory biomarkers for more effective predictive models. Recent studies have also suggested that risk scales like SUDEP-3 and SUDEP-7 could be useful, but lack sensitivity to identify high risk patients in broader clinical contexts [7]. Therefore, the need for large scale prospective studies to solve these limitations and develop preventive interventions is imperative.

We considered that certain factors like clinical, electroencephalographic and genetical characteristics were highly associated with increased risk of SUDEP. Taking this into account, a key question arises: Which risk factors can be identified in scientific literature as adamant for developing SUDEP in patients with seizures?.

The purpose of this study is creating a scientific systematic literature review to summarize evidence regarding risk factors associated with SUDEP in epileptic patients. This review also aims to solve literature inconsistencies, identify research gaps and provide clinical strategies to prevent SUDEP.

A systematic literature review will be executed using PRISMA guidelines to answer this key question. An exhaustive literature search will be made using relevant biomedical databases such as PubMed, Embase and The Cochrane Library to identify observational studies and clinical trials that explore SUDEP risk factors. Lastly, we will make a qualitative and quantitative analysis of the results to provide an updated overview of the risk factors that increase chances of developing SUDEP in these patients.

This study will also contribute to the current understanding of SUDEP and provide evidence-based treatments to reduce incidence in order to improve quality of life and survival of epileptic patients.

Methods

Study Type

This systematic literature review was designed to identify, synthesize and evaluate available incidence data of risk factors associated with sudden unexpected death in epilepsy (SUDEP). We included observational studies (cohort, case control and case series studies) which analyzed associations between specific risk factors and the ocurrence of SUDEP.

Selection Criteria

Study Types

We included observational studies (cohort, case control and case series studies) published in English or Spanish, with statistical analysis on the relation between risk factors and SUDEP. We excluded narrative reviews, editorials and studies that lacked methodological details.

Participants

Participants of this study included any patients diagnosed with epilepsy, with no age, comorbidities or sex restrictions, that were evaluated in primary studies in which SUDEP was defined as a clinical outcome.

Interventions/Exposition

Expositions for our study were clinical, demographic and electrophysiological characteristics. We also took into account epilepsy treatment, type of epilepsy, crises frequency, psychiatric comorbidities and adherence to treatment.

Outcomes

Primary Outcomes

SUDEP, defined by the international consensus criteria.

Secondary Outcomes

Specific risk factors associations (such as generalized tonic-clonic seizures, anticonvulsant polytherapy, or age of epilepsy onset) and the incidence of SUDEP.

Search Methods for Primary Studies Identification

Electronic Databases and Search Strategy

A systematic search was made in these electronic databases: PubMed, Embase, Cochrane Library and Scopus. Search strategy included terms such as “SUDEP”, “risk factors” and “epilepsy”, using boolean operators and filters. Complete search strategy details are described in the annex.

Other Resources

We checked references from included studies and read abstracts from relevant congresses. We also made a search in clinical trials records to identify non-published studies.

Data Gathering and Analysis

Study Selection

Two independent reviewers evaluated titles and abstracts recovered from searches. Potentially relevant full text articles were reviewed to evaluate their eligibility according to preset criteria.

Data Extraction and Management

Two independent reviewers extracted data using a standardized form. Extracted data included participants´characteristics, definition of risk factors which were evaluated, statistical methods and reported outcomes. Discrepancies were solved by consensus or a third reviewer.

Study Evaluation Using Critical Appraisal Tools

We used tools such as Newcastle-Ottawa Scale (NOS) for observational studies, evaluating details like selection, comparability and exposition.

Bias Control

Missing data Management

Studies with significant missing data in critical variables were excluded. We tried to make contact with authors to obtain additional information when it was possible.

Results

A total of 348 registries were identified by electronic records and database searches. We excluded 315 registries that did not meet selection criteria. We afterwards evaluated 28 text-complete studies, in which 2 were excluded by not meeting preset inclusion criteria. Finally, we included 26 studies that met criteria for this review.

Details from the process of identification, screening and study selection is presented in a PRISMA flow chart (Figure 1).

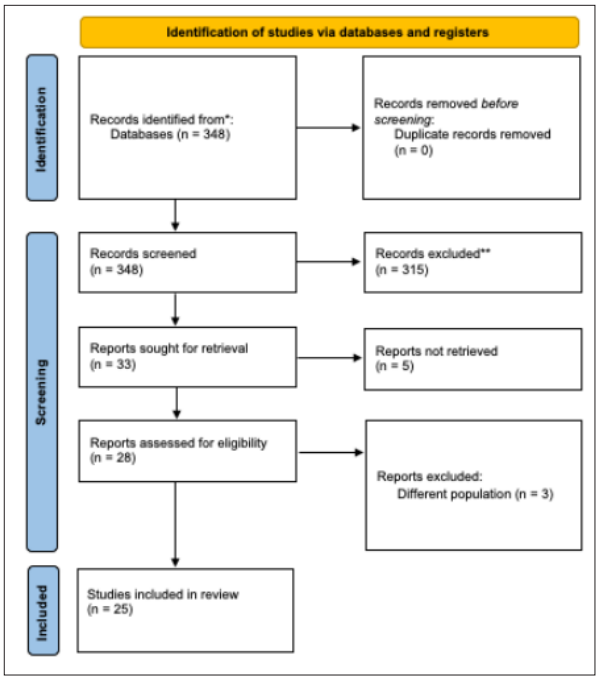

Figure 1: PRISMA Flow Chart

The studies included in this review encompassed various aspects of the tumor microenvironment (TME) in lymphomas and chronic lymphocytic leukemia (CLL). A total of 17 studies were evaluated, divided into different methodological designs: cohorts (n = 13), narrative reviews (n = 2), systematic reviews (n = 1), and a clinical trial (n = 1). Sample sizes varied widely, ranging from fewer than 50 participants to meta-analyses that included over 3,000 patients.

For lymphomas, the studies primarily focused on diffuse large B-cell lymphoma (DLBCL, n = 7), follicular lymphoma (FL, n = 5), mantle cell lymphoma (MCL, n = 1), and classical Hodgkin lymphoma (cHL, n = 2). Within these, immunological profiles of the TME were investigated, such as the expression of specific biomarkers (e.g., IL-6, Tim-3+Foxp3+Treg) and cellular composition (e.g., regulatory and cytotoxic T lymphocytes). In DLBCL studies, such as those by Matias Autio et al. (n = 3 cohorts; 81, 51, and 137 patients) and Weijie Zhong et al. (n = 50 tissue samples), the influence of the TME constitution on survival and chemotherapy response was demonstrated. In FL, the meta-analysis by Mixue Xie et al. included data from 23 studies with 3,336 patients, while the clinical trial by Thomas Menter et al. analyzed 154 participants divided into two treatment groups (n = 77 per group).

In CLL, three studies focused on aspects such as pyroptosis and TME modulation under treatment with BTK inhibitors and immunotherapy. For example, Sha et al. used 151 samples to construct and validate a prognostic model, and Puzzolo et al. analyzed the Th2/Th1 cell ratio in two cohorts of 71 patients each.

The studies' time horizons were diverse, with follow-ups ranging from 1 year to more than 12 years. For example, Peter Hollander et al.'s study on cHL reported a median follow-up of 12.9 years (n = 459), whereas in DLBCL, the study by Zhi-Zhang Yang et al. had a follow-up of up to 3 years (n = 82). Studies such as Qixiang Rong et al.'s on NK/T lymphoma reported a wide follow-up range (1–132 months; median = 43 months; n = 78).
The methodologies used included advanced techniques such as multi-omics analysis, immunohistochemistry, and flow cytometry [8-11]. These tools enabled a detailed characterization of cellular subtypes and biomarkers in the TME. Additionally, the studies reviewed multiple public databases, such as GEO, to integrate large cohorts, as seen in Tao Pan et al., which included 1,084 patients.

Risk of bias evaluation in case control studies is detailed in table 1,2. Most of the studies had low risk of bias in selection, comparability and exposition criteria. Nevertheless, some specific aspects showed concern areas.

Table 1: Characteristics of Included Studies

Author	Year	Country	Design	Objective	N	Participants	Time Horizon
Olafur Sveinsson, et al (3)	2020	Sweden	Case-control	Examine the hypothesis that certain clinical features increase the risk of sudden unexpected death in epilepsy (SUDEP)	255 SUDEP cases (confirmed and probable) and 1,148 controls	Patients with epilepsy, including generalized and focal forms; genetic, structural, infectious, and other causes	Observation of patients from 2006 to 2011
Olafur Sveinsson, et al (21)	2020	Sweden	Case-control	Assess the association between antiepileptic drug (AED) use, adherence, and other relevant medications with SUDEP risk	255 SUDEP cases and 1,148 matched controls	Patients diagnosed with epilepsy; cases were SUDEP deaths, controls were patients with epilepsy matched by sex and calendar time	Follow-up from 2006 to 2011
İpek Esen Melez, et al (17)	2017	Turkey	Case-control	Explore autopsy findings and available medical data for the differential diagnosis of SUDEP	112 patients with a previous epilepsy diagnosis	Mean age 34.2 years; sex distribution 66.1% men, 33.9% women	Cases collected between 2007 and 2011

Dale C. Hesdorffer, et al (22)	2011	USA, Sweden, UK (Scotland & England), etherlands	Case-control	Increase statistical power to identify SUDEP risk factors by analyzing combined case-control data	289 SUDEP cases and 958 controls (total: 1,247)	People with epilepsy, some with confirmed or probable SUDEP; controls were living people with epilepsy, including various ages, genders, and ethnicities	Data collected from 1980 to 1998 (depending on study)
Y. Langan, et al (18)	2005	United Kingdom	Case-control	Examine the influence of various factors on SUDEP risk in epilepsy patients	154 cases and 616 controls	Patients with active epilepsy, aged 16–50 years, who died suddenly and unexpectedly with no identified cause at autopsy; controls matched by age and location	Retrospective evaluation from 1989 to 1998
Nikolas Hitiris, et al (23)	2007	Scotland, United Kingdom	Case-control	Investigate the association between clinical features and SUDEP, with a focus on risk factors	62 SUDEP cases and 124 controls (2 controls per case)	Patients with refractory epilepsy treated at the Epilepsy Unit, aged 12–90 years	Follow-up period of 23 years (1982–2005)
Kelly C. Lear-Kaul, et al (24)	2005	United States	Case-control	Review the association between clinical variables and SUDEP to identify risk factors in epileptic patients	67	Epileptic patients, 48 men and 19 women, aged 2–58 years (mean 35.5 years). Many had long-standing epilepsy, mostly idiopathic (51%).	January 1993–December 2000 (Arapahoe County) and January 1996–September 2000 (Denver Medical Examiner)
L. Nilsson, et al (25)	1999	Sweden	Case-control	Investigate the association between clinical variables and SUDEP to identify risk factors	6,880 in the initial cohort; 57 SUDEP cases and 171 controls	Patients with epilepsy, aged 15–70 years, admitted to Stockholm hospitals between 1980–1989	Follow-up until 1991
Dag Aurlien, et al (26)	2012	Norway	Case-control	Estimate SUDEP incidence in Rogaland County, Norway, and evaluate whether lamotrigine use increases SUDEP risk in women or other epilepsy subgroups	26 SUDEP cases (16 definite, 3 probable, 7 possible) and 89 controls	Epilepsy patients from Rogaland, matched by age and sex	August 1995 to July 2005 (10 years)
Robert Kloster, et al (27)	1999	Norway	Case-control	Examine SUDEP risk factors and their potential role in death outcomes among epilepsy patients	140 patients (42 classified as SUDEP, 37 as non-SUDEP, and 61 excluded due to lack of autopsy)	Patients with chronic refractory epilepsy, mean age: 27.9 years (SUDEP), 32.6 years (non-SUDEP); mean epilepsy onset at 8.2 years (SUDEP) and 12.7 years (non-SUDEP)	Analysis of deaths between 1965 and 1996

Rohit Shankar, et al (28)	2016	United Kingdom	Case-control	Compare SUDEP risk factors between SUDEP cases and living controls using the "SUDEP and Seizure Safety Checklist"	48 SUDEP cases; 220 living controls	SUDEP cases: 48 patients (33 men, 15 women), mean age 42.5 years, range 2–82 years; controls: 220 epilepsy patients, mean age 42.76 years, range 9–86 years	9 years (2004–2012 for SUDEP cases), 1 year for controls (2013–2014)
Wen-wu Zhang, et al (29)	2016	China	Case-control	Examine SUDEP risk factors in patients with convulsive epilepsy in rural communities	35 probable SUDEP cases compared to 105 controls	Patients with convulsive epilepsy in rural western China	Mean 27.14 months (range 1–71 months)
Nikolas Hitiris, et al (23)	2007	United Kingdom (Scotland)	Case-control	Investigate the association between clinical features and SUDEP, focusing on likely risk factors	6,140 patients in cohort, 62 SUDEP cases analyzed and 124 living controls	Adult epilepsy patients treated at the Epilepsy Unit, Western Infirmary, Glasgow; onset age, seizure types, and treatments	Retrospective evaluation of 23 years (1982–2005)
Anders Gaarsdal Holst, et al (12)	2013	Denmark	Cohort	Determine SUDEP incidence and estimate the risk of all-cause and unexplained sudden death in epilepsy patients	3,034,974 subjects (33,022 with epilepsy and 3,001,952 without epilepsy)	Danish subjects aged 1–35 years (2000–2006); epilepsy cohort showed higher prevalence of comorbidities (neurological disease, psychiatric disorders, etc.)	7 years (2000–2006)
T.S. Walczak, et al (30)	2001	United States	Cohort	Determine the incidence and risk factors for sudden unexpected death in epilepsy (SUDEP)	4,578 patients	Patients diagnosed with epilepsy evaluated at three epilepsy centers (MINCEP Epilepsy Care, Mayo Clinic, Marshfield Clinic)	Follow-up period from June 1991 to December 1996
Kenneth Opeskin, et al (13)	2003	Australia	Cohort	Identify risk factors associated with SUDEP in a population of people with epilepsy	100 (50 SUDEP cases and 50 epilepsy controls who died from other causes)	Epileptic subjects who died in Victoria, Australia, between 1997 and 1999; differentiated into SUDEP deaths and deaths from natural causes or accidents	December 1997 to August 1999
Santoshi Billakota, et al (14)	2018	United States	Cross-sectional	Explore the relationship between peri-ictal cardiorespiratory dysfunction (CRD), sleep-disordered breathing (SDB), and neuroendocrine function in SUDEP clinical risk	30 patients	Adult epilepsy patients (20 women, 10 men), aged 35–70 in the high-risk SUDEP group and 23–57 in the low-risk group	Cross-sectional

Adam Strzelczyk, et al (15)	2016	Germany, Austria, itzerland	Cross-sectional	Examine attitudes toward SUDEP counseling and other epilepsy risk factors among neurologists and pediatric neurologists, identifying factors associated with lack of SUDEP discussion	519 neurologists and ropediatricians	Mean age: 45.5 years; 41.6% women; 66.9% adult neurologists, 31.0% pediatric neurologists	Large proportion of neurologists do not discuss SUDEP, contrasting with clinical guidelines. Lack of experience and skepticism toward prevention effectiveness are key factors. Promoting awareness and prevention strategies may increase the proportion of neurologists informing about SUDEP.
Christopher M. DeGiorgio, et al (31)	2018	United States	Narrative Review	Review the incidence, risk factors, biomarkers, and prevention strategies for SUDEP	-	Not applicable	Variable according to reviewed studies (from months to decades)
Teri B. O'Neal, Sanjay Shrestha, et al (32)	2022	United States	Narrative Review	Provide an update on SUDEP epidemiology, pathophysiology, risk factors, and treatment options to minimize its occurrence	-	Not applicable (narrative review)	Data based on studies published between 1987 and 2021
Robyn Whitney, et al (33)	2019	Canada	Narrative Review	Discuss SUDEP, emphasizing risk factors and its mitigation and prevention	-	People with epilepsy, including children and adults	General information without a specific time frame, focused on previous studies
S. Shorvon, et al (34)	1997	United Kingdom	Narrative Review	Identify risk factors associated with sudden unexpected death in epilepsy (SUDEP)	Three cohorts: 601 adults, 301 children, and 564 newly diagnosed epilepsy patients	Epilepsy patients, including adults with chronic epilepsy, children with epilepsy, and unselected cohorts of newly diagnosed epilepsy	Between 3 and 6.9 years, depending on the cohort
T.W. May and C.W. Israel (35)	2019	Germany	Systematic Review	Review SUDEP epidemiology, risk factors (especially cardiac), pathophysiological mechanisms, and prevention strategies	-	People with epilepsy, particularly those with treatment-resistant epilepsies and frequent generalized tonic-clonic seizures (GTCS)	Not applicable; based on previous studies and pidemiological data analysis

Y. Langan (36)	2000	United Kingdom	Systematic Review	Identify SUDEP risk factors through case-control studies and literature review	154 SUDEP cases identified for an ongoing case-control study, each matched with four controls	Patients with active epilepsy, mean age 32 years; majority were men (97 men and 57 women)	Historical data from 1980–1989; ongoing study in 2000
José F. Téllez-Zenteno, et al (16)	2005	Canada	Systematic Review	Provide an evidence-based analysis of SUDEP risk factors and incidence	404 citations identified, 83 articles reviewed in full, and 36 studies included in analysis	Patients with epilepsy (children and adults), including general population studies, epilepsy centers, etc.	Varies among included studies; some studies cover more than 10 years

Table 2: Risk of Bias Assessment for Case-Control Studies

Criterion	Olafur einsson, et al. [3]	Olafur einsson, et al. [21]	İpek Esen Melez, et al. [17]	Dale C. sdorffer, et al. [22]	Y. Langan, et al. [18]	Nikolas Hitiris, et al. [23]	Kelly C. Lear-Kaul, et al. [24]	L. Nilsson, et al. [25]	Dag Aurlien, et al. [26]	Robert Kloster, et al. [27]	Rohit Shankar, et al. [28]	Wen-wu Zhang, et al. [29]	Nikolas Hitiris, et al. [23]
Selection													
1) Is the case definition adequate?	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation (★)	a) Yes, with dependent validation using standard criteria and expert eurologist review (★)
2) Rsentativeness of the cases	a) Consecutive series or obviously representative (★)	a) Consecutive series or obviously presentative (★)	a) Consecutive series or obviously representative (★)	b) Potential selection bias or not indicated	a) Consecutive series or obviously epresentative (★)	a) Consecutive series or obviously presentative (★)	a) Consecutive series or obviously representative (★)	b) Potential selection bias or not indicated	a) Consecutive series or obviously representative (★)	a) Consecutive series or obviously epresentative (★)	b) Potential selection bias or not indicated	b) Potential selection bias or not indicated	b) Potential selection bias due to exclusion of patients with non-convulsive epilepsy or significant comorbidities
3) Selection of controls	a) Community controls (★)	a) Community controls (★)	a) Community controls (★)	a) Community controls (★)	a) Community controls (★)	a) Community controls (★)	a) Community controls (★)	c) No defined controls in the study design	a) Community controls (★)	a) Community controls (★)	c) No defined controls in the study design	a) ommunity controls (★)	a) Controls selected from the same rural base population, matched by age and sex (★)
4) Definition of controls	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)	b) No source description	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)	c) Not applicable	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)	c) Not applicable	a) No history of the disease (endpoint) (★)	a) No history of the disease (endpoint) (★)
Comparability													
1) Comparability of cases and controls	a) Study controls for frequency of generalized tonic-clonic seizures (GTCS) (★)	a) Study controls for frequency of GTCS (★)	a) Study controls for frequency of GTCS (★)	a) Study controls for age and sex (★)	a) Study controls for frequency of GTCS (★)	a) Study controls for frequency of GTCS (★)	a) Study controls for epilepsy duration and age at onset (★)	c) Not applicable	a) Study controls for seizure frequency (★)	a) Study controls for generalized tonic-clonic seizure frequency and AED type (★)	c) Not applicable	a) Study controls for key factors such as seizure frequency, treatment aherence, and nighttime uervision (★)	a) Study controls for seizure frequency and epilepsy duration (★)

b) Also controls for living conditions (★)	b) Also controls for living conditions and treatment adherence (★)	b) Also controls for living conditions and treatment adherence (★)	b) Also controls for living conditions and treatment adherence (★)	b) Also controls for epilepsy duration and age at onset (★)	b) Also controls for nighttime supervision (★)	b) Also controls for syndromic lassification (idiopathic, cryptogenic, etc.) (★)	b) Also controls for AED number and dose changes (★)						
Exposure													
1) Exposure ascertainment	a) Secure record (e.g., standardized medical records) (★)	a) Secure record (e.g., medical records and national databases) (★)	a) Secure record (e.g., medical records and national databases) (★)	a) ndardized medical records/ autopsies (★)	a) Secure record (e.g., reviews of medical records and standardized autopsies) (★)	b) Structured interviews and medical record reviews (★)	b) Structured medical record review and forensic reports (★)	b) Structured medical record review and autopsies (★)	a) Detailed review of medical and forensic records (★)	a) Medical records and autopsy reports (★)	a) Detailed review of medical records and autopsy findings (★)	a) ssessment using evidence-based Sndardized checklists (★)	a) Review through structured questionnaires, medical reports, and verbal autopsy interviews (★)
2) Same method for exposure determination	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)	b) Inconsistent between cases	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)	a) Yes (★)
3) Non-response rate	a) Same rate for both groups (★)	a) Same rate for both groups (★)	a) Same rate for both groups (★)	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described	b) Non-responders described

Case and Controls Selection

Case definition was appropriate in the majority of included studies, with an independent validation in all of them (★). However, representativeness of cases had a potential risk of bias in some of the included studies, mainly from the exclusion of patients who had non-epileptic seizures or important comorbidities, as seen in Hesdorffer et al. and Zhang et al studies. As for controls, most of the studies with defined controls used appropriate selecting methods from the community or the same base population (★), except in two studies in which source was not described or controls were not included in the study design.

Comparability

The majority of included studies were controlled taking into account crucial elements such as frequency of generalized tonic–clonic seizure (GTCS), adherence to treatment and life conditions, which made comparability appropriate between cases and controls (★). Some included studies like Aurlien et al., added additional variables like night time monitoring, while others did not include detailed adjustments, limiting their ability to control for potential confounders.

Exposure Determination

All included studies applied standardized methods for exposure determination based on clinical records, autopsies, and national databases (★). As for methods consistency, all of the studies, except for one, applied uniform methods for determining exposition in cases and controls. The non-response rate was described in several studies, but was not always equivalent between groups, which could introduce information bias in some cases.

The majority of studies had moderate to high methodological quality, with low risk of bias in most of the evaluated areas. However, some studies were presented with limitations in sample representativeness and controls´description, which could affect generalization of the results.

Risk of bias evaluation in cohort studies was included in table 3. Studies were varied in their population representativeness, comparability management, and participant follow-up.

Table 3: Risk of Bias Assessment in Cohort Studies

Criterion	Anders Gaarsdal Holst, et al (12)	T.S. Walczak, et al (30)	Kenneth Opeskin, et al (13)
Representativeness of the exposed cohort	a) Truly representative of the average epilepsy population in the community (★). The study included the entire young population of Denmark.	c) Selected group of users (e.g., patients from epilepsy centers) - The study included patients from three specialized epilepsy centers.	c) Selected group of users (e.g., individuals from coronial cases) - Cases were selected from autopsies conducted in a forensic context.
Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort (★). The non-exposed cohort also came from the national Danish population.	d) No description - A non-exposed cohort was not identified in the study design.	a) Drawn from the same community as the exposed cohort (★). Controls were selected from the same coronial case set.
Ascertainment of exposure	a) Secure record (e.g., registry data) (★). Highly reliable national Danish registry data were used to identify epilepsy.	a) Secure record (e.g., medical record, EEG data) (★). Exposure was documented through detailed clinical evaluations.	a) Secure record (e.g., forensic autopsies, medical and family reports) (★). Exposure was confirmed through multiple reliable sources.
Demonstration that outcome of interest was not present at the start of the study	a) Yes (★). Prior cases of sudden death and other confounding events were excluded.	a) Yes (★). Death cases were identified and classified prospectively from the study's start.	a) Yes (★). Deaths with known causes unrelated to SUDEP were excluded at the study's outset.

Comparability of cohorts on the basis of the design or analysis	a) Study controls for comorbidities (e.g., neurological, psychiatric, and congenital conditions, Charlson score) (★). b) Study controls for additional factors (e.g., sex) (★).	a) Study controls for seizure frequency and type (tonic-clonic seizures identified as key factors) (★). The analysis adjusted for seizure frequency and other factors.	a) Study controls for key factors (e.g., age, sex, seizure type) (★). b) Study controls for additional factors (e.g., compliance with AEDs) (★).
Assessment of outcome	a) Independent blind assessment (★). Deaths were verified and classified through a comprehensive review by independent experts.	a) Independent blind assessment (★). Death cases were reviewed by an independent committee using standardized criteria.	a) Independent blind assessment (★). Deaths were assessed by a neuropathologist and an independent team.
Was follow-up long enough for outcomes to occur	a) Yes (★). Follow-up lasted up to 7 years, sufficient to observe the incidence of sudden death in epilepsy.	a) Yes (★). The follow-up included 16,463 person-years, sufficient to detect SUDEP.	Not applicable - The study was based on retrospective death cases, not prospective follow-up.
Adequacy of follow-up of cohorts	a) Complete follow-up - all subjects accounted for (★). The methodology allowed complete follow-up using national registries.	b) Subjects lost to follow-up unlikely to introduce bias (estimated rate <5%) (★). Most patients remained under follow-up.	d) No statement - Information regarding potential losses or limitations in cohort follow-up is not described.

Representativeness of Exposed and Non-Exposed Cohorts

The Holst et al. study included a representative cohort of Denmark´s young population, while Walczeck et al. and Opeskin et al. studies were based on selected groups with patients from seizure specialized facilities or forensic cases. As for non-exposed cohorts, only the Holst et al. and Opeskin et al. studies selected controls from the same base population while Walczak et al. did not described a non-exposed cohort [6,12].

Exposure Determination

All studies used robust and feasible methods for exposure determination. Holst et al. used Danish national records, while Walczak et al. and Opeskin et al. studies used medical records, electroencephalograms, forensic autopsies and family reports [6,13].

Outcome Presence at the Start of the Study

The three studies excluded previous cases of sudden death and other events that could bias the results, assuring that the interest outcome (SUDEP) was not at the start of follow-up.

Cohort Comparability

All included studies were controlled by key factors from design or analysis. For example, in Holst et al. authors adjusted by neurological, psychiatric and congenital comorbidities and other additional factors like sex. Walczak et al. and Opeskin et al. controlled by crises frequency, type of crisis (specially tonic-clonic) and anticonvulsant medication adherence.

Outcome Evaluation

The three studies employed blinded and independent evaluations to classify deaths related to SUDEP. In the Opeskin et al. study, deaths were evaluated by a neuropathologist along with an independent team.

Follow up time and Adequation

Prospective follow up in Holst et al. and Walczak et al. studies was enough to note SUDEP incidence, with follow up periods up to 7 years and over 16,000 years-patients, respectively [6,12]. However, the Opeskin et al. study was based on retrospective cases and did not include prospective follow up. Additionally, Holst et al. had complete follow up of participants due to national records, while Walczak et al. reported minimal losses (<5%) and Opeskin et al. did not specify follow up information.

In conclusion, Holst et al. and Walczak et al. studies showed high methodological quality, with low risk of bias in the majority of evaluated areas. However, the retrospective design in Opeskin et al. and the lack of detailed information on follow up losses showed limitations that might affect result interpretation.

Risk of bias evaluation of cross-sectional studies was summarized in table 4. Both studies showed methodological strengths, but they also had limitations that should be taken into account when analysing results.

Table 4: Risk of Bias Assessment in Cross-Sectional Studies

Item	Santoshi Billakota, et al (14)	Adam Strzelczyk, et al (15)
Sample representativeness	1 (The sample is representative of the target population: epilepsy patients in a monitoring unit at a tertiary center)	1 (The sample included broad representation of neurologists and pediatric neurologists from Austria, Germany, and Switzerland, although the low response rate could limit representativeness)
Sample size	0 (The sample size was not explicitly justified in statistical terms)	0 (The sample size was not explicitly justified in statistical terms, although ~5,000 physicians were contacted)
Excluded subjects	1 (Reasons for exclusion were described, and the exclusion rate was not high)	1 (Characteristics of participants and reasons for exclusion were described, with a reasonable response completion rate)
Group comparability (adjustment for age/ gender and additional confounders)	1 (Adjusted for gender and some relevant factors, but other potential confounders were not fully controlled)	1 (Partially adjusted for factors such as specialty, years of practice, and previous experience with SUDEP, but additional relevant confounders were not controlled)
Outcome assessment	1 (The primary outcome was assessed using appropriate methods, although blind evaluation was not mentioned)	1 (The primary outcome was assessed using self-reported questionnaires, appropriate for the design but susceptible to social desirability bias)
Statistical tests	1 (Statistical tests used were described, with confidence intervals and p-values included)	1 (Statistical tests used were described, with univariate and multivariate analyses included)

Sample Representativeness

Both studies included samples which were appropriate to their objectives. Billakota et al. evaluated epileptic patients in a follow up unit from a tertiary centre, assuring representativeness for this specific population. As for Strzelczyk et al., authors included a high representation of neurologist and neuro pediatricians from Austria, Germany and Switzerland, but the low answer rate can limit representativeness in their results.

Sample Size

None of the studies explained sample size in statistical terms. Billakota et al. included a limited number of patients in their sample, while Strzcelcyz et al. contacted 5,000 physicians approximately, but did not justify the final sample size [14,15].

Non included Subjects

Both studies described reasons for exclusion and showed reasonable completion rates. In Billakota et al., exclusion percent was not high and in Strzelczyk et al., participants´characteristics were described in both included and excluded, which contributed to it being methodologically transparent [14,15].

Groups Comparability

In both studies, partial adjustments were made by relevant factors. Billakota et al., controlled by sex and other key factors, while Strzelczyk et al. adjusted variables like specialty, practice years and previous experience with SUDEP, however other possible confounders were not exhaustively managed [14,15].

Outcome Evaluation

Methods used to assess outcomes were correctly made for each study design. Billakota et al., employed appropriate tools, but did not mention blind evaluation, while Strzelczey et al., used informed questionnaires, while appropriate for cross-sectional studies, could be a source of social-desirability bias [14,15].

Statistical Tests

Both studies appropriately described statistical tests that were used and reported confidence intervals and significance values. In Strzelczyk et al., univariate and multivariate analysis were included, strengthening results validity [15]. Risk of bias assessment in systematic reviews is detailed in table 5.

Evaluated domains include eligibility, identification and study selection criteria, data gathering and evaluation, synthesis and results. Findings show important concerns in various methodological aspects from the systematic review.

Table 5: Risk of Bias Assessment in Systematic Reviews

Domain 1: Study Eligibility Criteria	T.W. May and C.W. Israel (35)	Y. Langan (36)	José F. Téllez-Zenteno, et al (16)
Question	Response	Response	Response
1.1 Did the review follow pre-established objectives and eligibility criteria?	Probably not	Probably yes	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes	Yes	Yes
1.3 Were the eligibility criteria clearly defined without ambiguity?	Probably not	Probably not	Probably yes
1.4 Were all restrictions on eligibility criteria based on study characteristics appropriate?	Probably yes	Yes	Probably yes
1.5 Were restrictions on eligibility criteria based on information sources appropriate?	Probably not	Probably not	Probably not
1.6 Concerns regarding the specification of eligibility criteria	High	Moderate	Moderate
Domain 2: Identification and Selection of Studies	Response	Response	Response
2.1 Did the search include an appropriate range of electronic databases/sources?	Yes	Probably yes	Yes
2.2 Were additional methods used beyond database searching?	Probably not	Probably not	Probably yes
2.3 Did the search terms and strategy structure likely retrieve as many eligible studies as possible?	Probably yes	Probably not	Probably not
2.4 Were restrictions based on date, publication format, or language appropriate?	No	No	No
2.5 Were efforts made to minimize errors in study selection?	Probably yes	Probably yes	Yes
2.6 Concerns regarding the methods used to identify or select studies	High	Moderate	Moderate
Domain 3: Data Collection and Study Evaluation	Response	Response	Response
3.1 Were efforts made to minimize errors in data collection?	Probably yes	Probably yes	Yes
3.2 Were sufficient study characteristics available to interpret the results?	Yes	Yes	Yes
3.3 Were all relevant study outcomes collected for use in the synthesis?	Probably yes	Probably yes	Yes
3.4 Was the risk of bias formally assessed using appropriate criteria?	No	No	Probably not
3.5 Were efforts made to minimize errors in risk of bias assessment?	No	No	Probably not
3.6 Concerns regarding the methods used to collect data and assess studies	High	Moderate	Moderate
Domain 4: Synthesis and Results	Response	Response	Response
4.1 Did the synthesis include all studies it should?	Probably yes	Probably not	Yes
4.2 Were all pre-specified analyses reported, or were deviations explained?	Probably not	Probably not	Probably not
4.3 Was the synthesis appropriate given the nature and similarity of the research questions and outcomes?	Yes	Yes	Yes
4.4 Was variation between studies minimal or addressed in the synthesis?	Probably yes	Probably yes	Probably yes
4.5 Were the results robust?	Probably not	Probably not	Probably not
4.6 Were biases in the primary studies minimal or addressed in the synthesis?	No	No	No
4.7 Concerns regarding synthesis and results	High	Moderate	Moderate

Domain 1: Eligibility Criteria
In general terms, study eligibility criteria were appropriate to answer review questions. However, only the Téllez-Zenteno et al. review showed clear, unambiguous predefined criteria and objectives, which minimized risk of bias for this domain [16]. The May e Israel and Langan reviews showed ambiguity in eligibility criteria, with unclear restrictions to information sources, which led to moderate to high preoccupations on eligibility criteria specificity.

Domain 2: Identification and Study Selection
Search strategy was robust in the May e Israel and Téllez-Zenteno et al. reviews, by including a wide range of electronic databases [16]. However, only Téllez-Zenteno et al. employed additional methods like manual reference review to improve relevant study identification [16]. Language, date and publication format-based restrictions were inappropriate in all reviews, which may limit inclusion of relevant studies. For this domain May e Israel were assessed with high preoccupations while the other reviews as moderate.

Domain 3: Data Gathering and Study Evaluation
Efforts to minimize data gathering errors were evident in all systematic reviews, even though risk of bias assessment in primary studies was insufficient in the three of them. This meant a significant limitation in terms of ensuring quality and credibility of included synthesized data. As a result, May e Israel review was met with high preoccupations and moderate in the other two reviews.

Domain 4: Synthesis and Results
The Téllez-Zenteno et al. review presented the most complete data synthesis, including all relevant studies [16]. However, none of the reviews reported consistently predefined analysis, and did not correctly assess bias from the primary studies. Even though inter-study variability was discussed in all three reviews, general results were not solid due to these methodological limitations. For May e Israel review preoccupations were classified as high, while Langan and Téllez-Zenteno et al. as moderate.

Table 6 summarizes main findings of the included studies and were grouped by methodological design, intervention or risk factor, comparator, evaluated outcomes and reported results. They proposed an integral vision on risk factors associated with SUDEP and their determinants.

Table 6: Results of Included Studies

Author	Year	Design	Risk Factor	Comparator	Outcomes	Results
Olafur Sveinsson, et al (3)	2020	Case-Control	Generalized tonic-clonic seizures (GTCS), living alone, substance abuse, alcohol dependence	Participants with epilepsy without GTCS history or with nighttime supervision	- SUDEP in relation to seizure type and frequency	GTCS in the past year: OR 26.81 (95% CI: 14.86–48.38) vs. no GTCS
					- Living conditions	- Nocturnal GTCS in the past year: OR 15.31 (95% CI: 9.57–24.47)
					- Education	- Frequency of GTCS:
					- Comorbidities	1–3 GTCS/year: OR 22.14 (95% CI: 12.74–38.46)
						4–10 GTCS/year: OR 31.87 (95% CI: 15.95–63.67)
						- Living alone without sharing a room: OR 5.01 (95% CI: 2.93–8.57) vs. room sharing
Olafur Sveinsson, et al (21)	2020	Case-Control	Use of antiepileptic drugs (monotherapy, polytherapy), treatment adherence, and use of other medications (antidepressants, beta-blockers, statins)	Patients without recent antiepileptic treatment (no AEDs)	SUDEP risk associated with monotherapy, polytherapy, AED adherence, and other drugs (statins, beta-blockers, antidepressants)	- Polytherapy with ≥3 AEDs: Significantly reduced SUDEP risk (OR 0.31, 95% CI: 0.14–0.67).
						- Levetiracetam in monotherapy: Associated with the lowest SUDEP risk (OR 0.10, 95% CI: 0.02–0.61).
						- Lamotrigine in polytherapy: Reduced SUDEP risk (OR 0.55, 95% CI: 0.31–0.97).

						- Valproic acid in polytherapy: Reduced SUDEP risk (OR 0.53, 95% CI: 0.29–0.98).
						- Non-adherence: Increased SUDEP risk (OR 2.75, 95% CI: 1.58–4.78).
						- Statin use: Reduced SUDEP risk (OR 0.34, 95% CI: 0.11–0.99).
İpek Esen Melez, et al (17)	2017	Case-Control	Inconsistent antiepileptic drug use, cardiac conditions (hypertrophy, fibrosis), age, and gender	Patients with other causes of death (cardiovascular disease, other natural causes, undetermined)	Cause of death (SUDEP vs. other causes), autopsy anatomical and toxicological findings	- Causes of death distribution: 40 cases (35.7%) SUDEP, 14 cases (12.5%) cardiovascular disease, 10 cases (8.9%) other natural diseases, 20 cases (17.9%) unnatural causes, and 28 cases (25%) undetermined causes.
						- SUDEP gender and age: 21 men and 19 women, mean age 30.6 ± 13.3 years.
						- External signs of seizure in SUDEP: 72.5% (29 cases) had external signs like tongue injuries.
						- Brain and lung edema in SUDEP: Brain edema (60%) and lung edema (92.5%), coexisting in 60%.
						- Toxicology analysis in SUDEP: 55.3% (21 cases) without antiepileptics detected; 44.7% had AEDs (12 monotherapy, 5 polytherapy).
						- Heart weight: 47.5% of SUDEP cases had overweight hearts vs. 100% in cardiovascular deaths.
						- Fibrosis/hypertrophy in SUDEP: Found in 40% vs. 100% in cardiovascular deaths (p=0.001).
Dale C. Hesdorffer, et al (22)	2011	Case-Control	GTCS frequency, polytherapy with antiepileptic drugs (AEDs), epilepsy duration, early onset age, lamotrigine therapy	Patients with epilepsy without SUDEP	Confirmed or probable SUDEP	- GTCS frequency and SUDEP risk:
						No GTCS: reference
						1–2 GTCS/year: OR 2.94
						3–12 GTCS/year: OR 8.28
						13–50 GTCS/year: OR 9.06
						>50 GTCS/year: OR 14.51
						- AED Therapy:
						Monotherapy: OR 0.74 (protective but not statistically significant).
						Polytherapy: OR 1.95, significant risk increase.

						- Early epilepsy onset (<16 years): OR 1.72.
						- Epilepsy duration (>15 years): OR 1.95.
						- Gender: Male OR 1.42.
						- Lamotrigine in idiopathic generalized epilepsy: OR 1.86, increased SUDEP risk.
Y. Langan, et al (18)	2005	Case-Control	Recent GTCS history, GTCS frequency, use of ≥3 AEDs, carbamazepine use, lack of nighttime supervision	Controls with epilepsy without recent seizure history or specified risk factors	SUDEP (Sudden Unexpected Death in Epilepsy)	- Recent GTCS history: OR 13.8 (95% CI: 6.6–29.1) vs. no GTCS.
						- GTCS frequency in the last 3 months:
						0–5 seizures: Reference
						6–10 seizures: OR 0.7 (95% CI: 0.2–2.5), not significant.
						11–20 seizures: OR 19.4 (95% CI: 1.7–226).
						21–50 seizures: OR 14.6 (95% CI: 1.3–165).
						>50 seizures: OR 11.7 (95% CI: 0.3–419), not significant.
						- Use of ≥4 AEDs: OR 3.1 (95% CI: 1.4–7.0).
						- No AED use or unknown history: OR 21.7 (95% CI: 4.4–106).
						- Carbamazepine use: OR 2.0 (95% CI: 1.1–3.8).
						- Nighttime supervision: Same room OR 0.4 (95% CI: 0.2–0.8); special devices OR 0.1 (95% CI: 0.0–0.3), protective effect.
						- Asthma history: OR 0.2 (95% CI: 0.1–0.9), protective effect.
Nikolas Hitiris, et al (23)	2007	Case-Control	Epilepsy duration, recent seizures, epilepsy type	Patients with epilepsy without SUDEP	SUDEP incidence in relation to clinical and treatment variables	- Average age of death in SUDEP: 36 years.
						- Age distribution: 80% of SUDEP cases were ≤45 years.
						- Average epilepsy duration in SUDEP cases: 18 years vs. 11 years in controls (p = 0.001).
						- Recent seizure history: Significantly higher in SUDEP cases than in controls (p = 0.007).
						- Tonic-clonic seizures: Present in >90% of SUDEP cases, but no direct statistical association with SUDEP risk.

						- Carbamazepine use: No significant association with SUDEP risk.
						- Place of death: 97% (60/62) of SUDEP cases died at home; 59/62 found in bed.
						- Witnessed cases: Only 3 cases observed, showing facial cyanosis and respiratory difficulty.
Kelly C. Lear-Kaul, et al (24)	2005	Case-Control	Antiepileptic drug levels, epilepsy duration, recent stress factors, gender, and age	Not specified	Risk factors associated with SUDEP, including clinical, toxicological, and demographic data	- Antiepileptic drug levels: Of 54 patients receiving treatment, 67% had subtherapeutic levels, 22% therapeutic levels, and 7% undetectable levels.
						- Adherence history: Poor adherence in 24% of cases; 10 patients were not receiving AEDs.
						- Epilepsy duration: Mean of 18.4 years (range: 4 months to 53 years).
						- Age: Mean 35.5 years; male-to-female ratio 3:1 (72% men).
						- Epilepsy type: Idiopathic in 51%, post-traumatic in 21%, and mixed/unknown causes in others.
						- Place of death: 87% died at home; 57% in bed or on a sofa; 67% found in a prone position.
						- Seizure-related injuries: Evidence of seizures (e.g., tongue laceration) in 58% of cases.
						- Recent stress factors: Present in 53% of cases (e.g., infections, fatigue, life changes).
						- Pulmonary edema: Found in 51% of autopsies, suggesting respiratory inhibition as a cause.
L. Nilsson, et al (25)	1999	Case-Control	Seizure frequency, number of antiepileptic drugs, epilepsy onset age, dosage changes	Patients with epilepsy without SUDEP	SUDEP incidence, seizure frequency, epilepsy types, comorbidities (e.g., dementia)	- Seizure frequency in the past year:
						0–2 seizures/year: RR = 1.00 (reference group)
						3–12 seizures/year: RR = 7.21 (95% CI: 2.52–20.60)
						13–50 seizures/year: RR = 8.64 (95% CI: 2.88–25.93)
						>50 seizures/year: RR = 10.16 (95% CI: 2.94–35.18)

						- Number of AEDs (monotherapy vs. polytherapy):
						1 drug: RR = 1.00 (reference)
						2 drugs: RR = 2.69 (95% CI: 1.28–5.65)
						3 drugs: RR = 9.89 (95% CI: 3.20–30.60)
						- Epilepsy onset age:
						31–45 years: RR = 1.38 (95% CI: 0.43–4.40)
						16–30 years: RR = 2.34 (95% CI: 0.67–8.20)
						0–15 years: RR = 7.72 (95% CI: 2.13–27.96)
						- AED dose changes (last year):
						0 changes: RR = 1.00 (reference)
						1–2 changes: RR = 0.75 (95% CI: 0.36–1.53)
						3–5 changes: RR = 6.08 (95% CI: 1.99–18.56)
						- Comorbidities: Dementia: RR = 6.00 (95% CI: 1.50–23.99); CNS infections: RR = 1.53 (95% CI: 0.55–4.25); anxiolytic use (particularly in men): RR = 3.00 (95% CI: 1.16–7.76).
Dag Aurlien, et al (26)	2012	Case-Control	Lamotrigine (LTG) use	Patients with epilepsy not using LTG	SUDEP incidence, association of LTG with SUDEP risk in women, relationship with other factors	- SUDEP incidence with LTG: 3.9/1,000 person-years vs. 0.5/1,000 person-years without LTG ($p < 0.001$, incidence rate ratio [IRR]: 8.6; 95% CI: 3.3–21.5).
						- SUDEP incidence in women on LTG: 2.5/1,000 person-years vs. 0.5/1,000 in non-LTG users ($p = 0.007$, IRR: 5.0; 95% CI: 1.6–17.3).
						- Controls: 58.3% of women with definite/probable SUDEP were on LTG vs. 24.4% in controls ($p = 0.038$; OR: 5.6; 95% CI: 1.1–28.2).
						- Valproate (VPA): SUDEP incidence 1.2/1,000 person-years (95% CI: 0.6–4.8) vs. 0.6/1,000 without VPA ($p = 0.278$).
						- Carbamazepine (CBZ): SUDEP incidence 0.6/1,000 with CBZ vs. 0.8/1,000 without CBZ ($p = 0.504$).

Robert Kloster, et al (27)	1999	Case-Control	SUDEP risk factors: seizure frequency, body position at death, AED use, sleep relationship, seizure signs before death	Non-SUDEP group with defined causes of death (e.g., pneumonia, heart disease, status epilepticus, suicide, drowning)	SUDEP mortality and comparison with known-cause mortality; factors such as seizure type, frequency, body position at death, AED levels, comorbidities	- Seizure frequency: High frequency (>12 seizures/ year) in both groups: 32 cases in SUDEP, 26 in non-SUDEP.
						- Seizure type: Generalized motor seizures in all SUDEP cases; significant difference between groups (p=0.03).
						- Seizure signs before death: Observed in 67% of SUDEP cases (e.g., fresh tongue bites, cyanosis, seizure sounds).
						- Body position at death: Prone position in 71% of SUDEP cases; significantly higher than other positions (p=0.001).
						- Relationship with sleep: 60% of SUDEP cases occurred during sleep.
						- Brain pathology: 71% of SUDEP cases showed pathological changes (e.g., brain edema).
						- Heart pathology: Non-lethal changes in 33% of SUDEP cases.
						- Pulmonary pathology: Pulmonary edema present in 62% of SUDEP cases vs. 27% in non-SUDEP cases.
						- AED levels: 57% of SUDEP cases had subtherapeutic levels; toxicity was observed in one case (non-lethal).
Rohit Shankar, et al (28)	2016	Case-Control	Specific SUDEP risk factors (modifiable and non-modifiable) evaluated using the SUDEP and Seizure Safety Checklist	Living controls from a continuous sample of epilepsy patients at Cornwall clinics	Association of SUDEP risk factors; comparison of factors between cases and controls; calculation of odds ratios for each factor	- Prone sleeping position: OR = 0.034; 95% CI: [0.012, 0.094]; $p < 0.001$*
						- Unclear treatment history: OR = 0.03; 95% CI: [0.01, 0.1]; $p < 0.001$*
						- Generalized tonic-clonic epilepsy: OR = 0.03; 95% CI: [0.01, 0.09]; $p < 0.001$*
						- Increased seizure frequency: OR = 0.05; 95% CI: [0.02, 0.14]; $p < 0.001$*

						- Treatment adherence issues: OR = 0.09; 95% CI: [0.03, 0.23]; p < 0.001*
						- Alcohol misuse: OR = 0.10; 95% CI: [0.04, 0.28]; p < 0.001*
						- Subtherapeutic AED levels: OR = 0.08; 95% CI: [0.025, 0.24]; p < 0.001*
						- No nighttime supervision: OR = 13.0; 95% CI: [3.7, 45.26]; p < 0.001*
						- Epilepsy duration >15 years: OR = 0.22; 95% CI: [0.10, 0.49]; p < 0.001*
Wen-wu Zhang, et al (29)	2016	Case-Control	Early epilepsy onset, high seizure frequency, recent seizures	Patients with convulsive epilepsy without SUDEP	Probability of probable SUDEP	- Epilepsy onset age ≤10 years: OR = 6.8 (95% CI: 1.5–32.6).
						- Baseline seizure frequency >10 seizures/year: OR = 5.9 (95% CI: 2.2–16.6).
						- Seizures in the previous month: OR = 9.5 (95% CI: 3.0–30.1).
Nikolas Hitiris, et al (23)	2007	Case-Control	Epilepsy duration, seizure frequency, treatment type (polytherapy or carbamazepine use)	Matched living controls by year of birth, gender, and syndrome classification (idiopathic, cryptogenic, symptomatic)	SUDEP mortality; correlation with epilepsy duration, seizure frequency, treatment type	- SUDEP accounted for 11.7% of all deaths in the cohort (62/529 deaths).
						- Average epilepsy duration in SUDEP cases: 18 years vs. 11 years in controls (p = 0.001).
						- Seizures in the past year: Significantly higher in SUDEP cases (p = 0.007).
						- Mean age at death for SUDEP cases: 36 years; 80% of cases were under 45 years.
						- Gender: 36 men (58%) and 26 women (42%) among SUDEP cases.
						- Syndrome classification: Idiopathic 14.5%, Cryptogenic 75.8%, Symptomatic 9.7%.
						- Association with tonic-clonic seizures, polytherapy, or carbamazepine use: Not statistically significant.
						- Place of death: 97% (60/62) died at home; 59/62 found in bed.
						- Witnessed SUDEP cases: 3 cases showed facial cyanosis and respiratory difficulty during seizures.

Anders Gaarsdal Holst, et al (12)	2013	Cohort	Epilepsy diagnosis	Population without epilepsy	Risk of all-cause death and unexplained sudden death (SUD), including specific SUDEP cases	- SUDEP incidence in epilepsy:
						Definite/probable SUDEP: 41.1 per 100,000 person-years (95% CI: 31.6–54.9).
						All SUDEP cases: 72.4 per 100,000 person-years (95% CI: 58.7–89.4).
						- Age-specific incidence:
						1–18 years: 17.6 per 100,000 person-years (95% CI: 9.5–32.8).
						24–35 years: 73.8 per 100,000 person-years (95% CI: 52.5–103.8).
						- Risk of all-cause death: HR 5.4 (95% CI: 4.9–6.0), adjusted for age, sex, Charlson index, neurological, psychiatric, and congenital comorbidities.
						- Risk of unexplained sudden death (SUD): HR 16.3 (95% CI: 9.8–26.9), adjusted for the same factors.
						- SUDEP distribution by comorbidity: 54% of definite/probable SUDEP cases had no comorbidities.
T.S. Walczak, et al (30)	2001	Cohort	Seizure frequency/type, AED treatment, intellectual disability, epilepsy duration, structural brain lesions	Matched controls from the same epilepsy centers	SUDEP incidence, seizure frequency, IQ level, AED use, epilepsy duration, structural lesions	- SUDEP incidence: 1.21 per 1,000 person-years.
						- Gender: Higher incidence in women (1.45/1,000) vs. men (0.98/1,000).
						- Seizure frequency: Increased risk with >50 seizures/month (OR = 11.5; 95% CI: 1.3–99.3); lower frequencies were not significant.
						- Tonic-clonic seizures (GTCS): Increased risk: 1–3 GTCS/year (OR = 2.4), >3 GTCS/year (OR = 8.1; 95% CI: 2.2–30.0).
						- Intellectual disability (IQ <70): OR = 5.0 (95% CI: 1.3–19.3).
						- Polytherapy (>2 AEDs): OR = 3.8 (95% CI: 1.4–11.7).

						- Epilepsy duration ≥30 years: OR = 13.9 (95% CI: 3.4–57.1).
						- Structural brain lesions and psychotropic medication use: No significant associations.
Kenneth Opeskin, et al (13)	2003	Cohort	Epilepsy and associated risk factors: age, gender, seizure type/frequency, intellectual disability, AED use, substance abuse	Epileptic patients who died from non-SUDEP causes	SUDEP mortality and relationship with age, seizures, AED use, adherence, and circumstances of death	- Age: SUDEP cases were younger (mean 34.6 years) compared to controls (mean 40.9 years).
						- Gender: SUDEP cases were 54% male vs. 78% male in controls (significant).
						- Epilepsy duration: Similar in both groups (16.8 years in SUDEP vs. 18.8 years in controls).
						- Seizure frequency: Mean of 20.9 seizures in SUDEP vs. 6.5 in controls (greater variance in SUDEP group, with >50 seizures/year).
						- Seizure type: Generalized tonic-clonic seizures (30 in SUDEP, 27 in controls).
						- AED use: No significant difference in AED type or combination (common AEDs: carbamazepine, valproate, phenytoin).
						- Adherence: Poor adherence noted in 11 patients from each group.
						- Place of death: 48% of SUDEP cases died in bed at home vs. 32% of controls (significant).
						- Evidence of terminal seizures: More common in SUDEP (44% vs. 16% in controls, $p < 0.05$).
Santoshi Billakota, et al (14)	2018	Cross-Sectional	SUDEP risk assessment via SUDEP-7 inventory, peri-ictal cardiorespiratory dysfunction (CRD), sleep-disordered breathing (SDB), neuroendocrine dysfunction	Patients classified as low risk (SUDEP-7 = 0–2) and high risk (SUDEP-7 ≥3)	Presence of CRD, prevalence of SDB, neuroendocrine function	- Peri-ictal CRD: 60% of high-risk patients had CRD vs. 27% in low-risk ($p = 0.018$).
						- Hypoxemia and tachycardia occurred in all CRD patients; 5 high-risk patients had tachycardia, and 1 had bradycardia.

						- SDB: 88% of patients with evaluable PSG (7/8) showed SDB, including 1 with severe obstructive sleep apnea (AHI = 47.7), 1 with mild apnea (AHI = 13.4), and the remainder with elevated RDI values (1.1–3).
						- Neuroendocrine dysfunction: 35% of patients presented neuroendocrine abnormalities, predominantly men (p = 0.018). Testosterone and prolactin levels were outside the normal range, suggesting hormonal influence on SUDEP risk.
Adam Strzelczyk, et al (15)	2016	Cross-Sectional	SUDEP discussion in clinical practice	No formal comparator group	Frequency and factors influencing SUDEP discussions	- Frequency of SUDEP discussions:
						• 2.7% discuss SUDEP with all patients.
						• 8.7% discuss SUDEP in most patients (50–90%).
						• 20.8% discuss SUDEP occasionally (10–49%).
						• 44.5% discuss SUDEP rarely (1–9%).
						• 23.3% never discuss SUDEP.
						- Factors influencing discussions:
						• Lack of epilepsy training (OR: 3.67).
						• <10 years in practice (OR: 1.89).
						• Seeing <25 epilepsy patients per quarter (OR: 1.82).
						• Belief that discussions have no preventive consequences (OR: 1.78).
						- Other discussions:
						• Driving restrictions: 92.9% discuss with all patients.
						• Daily activity risks: 81.5% discuss with all patients.
						- Survey conducted August–October 2014.
Christopher M. DeGiorgio, et al (31)	2018	Narrative Review	Frequency of generalized tonic-clonic seizures (GTCS), AED use, sleep position, epilepsy duration, cardiac and EEG biomarkers	Patients at lower risk (e.g., fewer than 3 GTCS per year, AED use, non-prone sleep position, shorter epilepsy duration)	SUDEP incidence, risk factors, biomarkers, and prevention	- SUDEP incidence: 1.2 per 1,000 person-years in adults, 0.2–1.11 per 1,000 person-years in children.

						- GTCS frequency: Risk increases with >3 GTCS/ year: OR ranges between 7–12.1 (varies between studies).
						- Overall seizure burden (>13 seizures/year): OR 4.2.
						- Lack of AED use: OR 21.7; absence of treatment is a major risk factor.
						- Polytherapy (≥3 AEDs): OR 8.1, indicating severity of epilepsy.
						- Intellectual disability or IQ <70: OR 2.23–5.0.
						- Prone sleep position: Present in 73% of SUDEP cases, particularly in patients <40 years.
						- EEG/ECG biomarkers: Ictal tachycardia >80% of monitored seizures; prolonged PGES (postictal generalized EEG suppression) >80 seconds associated with 4x higher SUDEP risk.
						- Long epilepsy duration (>30 years): OR 13.9.
Teri B. O'Neal, Sanjay Shrestha, et al (32)	2022	Narrative Review	SUDEP risk factors, pathophysiological mechanisms (cardiac, autonomic, respiratory, and cerebral), and preventive options	No specific comparator group	SUDEP incidence, identification of risk factors, and intervention options	- SUDEP incidence: 1.2 cases per 1,000 person-years in the general epilepsy population; 6.3–9.3 cases per 1,000 person-years in drug-resistant epilepsy patients.
						- Lifetime risk: Up to 7% for all epilepsy patients and up to 12% in those with persistent epilepsy by age 40.
						- Risk factors:
						• GTCS: ≥3 GTCS/year or ≥13 total seizures/ year increase SUDEP risk significantly.
						• Age/gender: Higher incidence in young adults (20–40 years) and more frequent in males.
						• Polytherapy (≥3 AEDs): Associated with drug-resistant epilepsy and higher risk.
						- Other risks: Frequent AED dosage changes, nocturnal seizures, and untreated epilepsy.
						- Genetic risk: Mutations in SCN1A, KCNQ1, and other genes associated with epilepsy or cardiac arrhythmias.

Robyn Whitney, et al (33)	2019	Narrative Review	SUDEP risk factors and mitigation strategies	No formal comparator group	SUDEP risk and prevention in epilepsy patients	- GTCS risk:
						• Presence of GTCS: OR 10.
						• 1–2 GTCS/year: OR 5.07.
						• ≥3 GTCS/year: OR 15.46.
						- Risk mitigation factors:
						• Nighttime listening devices: OR 0.1, significantly reducing SUDEP risk.
						• Nighttime supervision: OR 0.4, also protective.
						- Refractory epilepsy: Failure to add AEDs in refractory epilepsy increases SUDEP risk (OR 6).
						- Time seizure-free: Failing to achieve seizure freedom for 1–5 years increases SUDEP risk (OR 4.7).
S. Shorvon, et al (34)	1997	Narrative Review	SUDEP risk factors in epilepsy patients	No specific comparator group	SUDEP rates, risk factors, and epilepsy-related mortality	- Adult cohort: Follow-up of 3,076 years with 1,849 patient-years total.
						• 24 deaths reported, 11 classified as SUDEP.
						• Standardized Mortality Rate (SMR): 5.1 (95% CI: 3.3–7.6).
						• SUDEP incidence: ~1:200 per year.
						- Pediatric cohort: Follow-up of 4,135 patient-years.
						• 28 deaths, 14 classified as sudden.
						• SMR: 15.9 (95% CI: 10.6–23.0).
						- Newly diagnosed cohort: Follow-up of 3,712 patient-years.
						• 114 deaths; no SUDEP cases reported.
T.W. May and C.W. Israel (35)	2019	Systematic Review	SUDEP risk factors: seizure frequency, AEDs, external factors (e.g., living alone, lack of monitoring)	People with epilepsy without SUDEP	SUDEP incidence and association with specific factors	- SUDEP incidence in adults: 1.2 per 1,000 person-years (PJ).
						- Drug-resistant epilepsy: SUDEP incidence up to 3.5 per 1,000 PJ.
						- Institutionalized/cognitively impaired patients: 4.2 per 1,000 PJ.
						- Video EEG monitoring candidates: Up to 6.2 per 1,000 PJ.
						- Children: SUDEP incidence lower, ~0.2–0.4 per 1,000 PJ, though older children (>12 years) have rates similar to adults.

						- GTCS frequency:
						• 1–2 GTCS/year: 500% risk increase.
						• >3 GTCS/year: 1,500% risk increase.
						- Sleep position: 73.3% of SUDEP cases occurred in prone position (85.7% in <40 years).
						- Nocturnal seizures: 3x higher SUDEP risk.
						- Living alone: 71% of SUDEP cases vs. 14% living with others.
Y. Langan (36)	2000	Systematic Review	SUDEP risk factors: age, gender, seizure frequency/type, AED changes, polytherapy, uncontrolled seizures, comorbidities	Matched controls by age and geographic location	SUDEP occurrence and associated risk factors	- Seizure frequency: RR = 10.16 (95% CI: 2.94–35.18) for >50 seizures/year compared to 2 seizures/year.
						- Polytherapy (≥3 AEDs): RR = 9.89 compared to monotherapy.
						- Frequent AED dose changes: RR = 6.08 (95% CI: 1.99–18.56).
						- Epilepsy onset age: RR = 18 for childhood onset vs. >45 years.
						- Dementia comorbidity: RR = 6 (95% CI: 1.5–23.99).
José F. Téllez-Zenteno, et al (16)	2005	Systematic Review	Multiple SUDEP risk factors	Non-SUDEP deaths and living epilepsy patients	SUDEP incidence and risk factors	- Annual SUDEP incidence: 0–10 per 1,000.
						- High-risk groups (epilepsy centers, surgery candidates): 2.2–10 per 1,000.
						- Low-risk groups (children/ general population): 0–1.35 per 1,000.

Case Control Studies

The Most Featured Studies Include those which Evaluated Risk Factors Like Generalized Tonic-Clonic Crises Frequency (GTCS), Life Conditions, Adherence to Treatment and the USE of Anticonvulsant Medication. For example:

- **Sveinsson, et al**. reported that having a GTCS in the last year increased significantly risk of SUDEP (OR 26.81, CI 95%: 14.86–48.38), specially in patients who lived alone and had no night time monitoring (OR 67.10, Ci 95%: 29.66–151.88). Moreover, substance abuse and alcohol dependence were associated with a higher risk [3].
- **Melez, et al**. found that 72.5% of SUDEP cases had external signs of crises like tongue wounds, and 60% has pulmonary and cerebral edema which might suggest an important paper as postictal state complications [17].
- **Langan, et al**. evidenced that night time monitoring was a protective factor, with an OR of 0.1 (CI 95%: 0.0–0.3) for night listening devices. They also showed that patients with more than 5 GTCS a year had a significant risk increase (OR 11.7, CI 95%: 0.3–419) [18].

Cohort Studies

Cohort Studies Estimated Sudep Incidence and Evaluated Related Factors:

- **Holst, et al. (2013)** showed an estimated incidence of SUDEP of 41.1 per 100,000 person-year for definitive and probable cases [12].
- **Walczak, et al. (2001)** found that longer times of diagnosed epilepsy (≥30 years) and use of multiple anticonvulsants (≥2) significantly increase the risk of SUDEP (OR 13.9 and OR 3.8, respectively) [6].

Cross-Sectional Studies

Cross Sectional Studies Explored Attitudes and Risk Related with Sudep in Specific Populations:

- **Billakota, et al. (2018)** observed that 60% of high risk of SUDEP patients had periictal cardiorespiratory dysfunction, while 88% showed evidence of sleep breathing disorders [14].
- **Strzelczyk, et al. (2016)** reported that 44.5% of neurologists discussed SUDEP in rare occasions, 23.3% never discussed it, making it a need for greater awareness in clinical practice [15].

Narrative and Systematic Reviews

Narrative and Systematic Reviews Provided a Broad Synthesis on Risk Factors:

- **Téllez-Zenteno, et al.** (2005) reported annual incidence of SUPED up to 10 per 1,000 person-year in high risk populations, while incidence in children was significantly lower (0-1.35 per 1,000 persons-year) [16].
- **May e Israel (2019)** explained that frequency of GTCS was a key determinant, with an increased risk of 1500% in patients with over 3 GTCS per year compared with those without crises [4].

Discussion

This study systematically reviewed literature to find and evaluate risk factors associated with SUDEP. Among all key findings, GTCS was the most important one along with lack of night time monitoring, inconsistent use of anticonvulsants and certain cardiac and respiratory biomarkers. Also, some factors such as frequency of GTCS and adherence to treatment were key for the incidence of SUDEP.

Alongside with previous studies, our findings highlight that recent GTCS increase significantly the risk of SUDEP, with an odds ratio (OR) up to 26.81 in patients with GTCS in the last year. These results align with the study findings of Sveinsson et al, which identified night GTCS and lack of night time monitoring combined drastically increased risk (OR: 67.10) [3].

Also, the lack of adherence to anticonvulsants was identified as an important risk factor (OR: 2.75), along with conclusions from Hesdorffer et al., which stressed the importance of maintaining adequate therapeutic levels of anticonvulsant medication to decrease this risk [19].

However, there are some discrepancies with the protective role of certain medications. For example, some studies report risk reduction with an adequate use of multiple anticonvulsants (Ex: Valproic acid, OR: 0.53). On the other hand, studies like Aurlien et al. suggest an increased risk with lamotrigine in women, probably due to methodological differences or by the studied population. Additionally, while night time monitoring has been associated as a protective factor, clinical implementation with devices such as alarms is still limited and paltry [20].

One of the strengths of this systematic review is the use of rigorous methodological criteria to select relevant studies and the assessment of risk of bias. Additionally, quantitative and qualitative analysis provides a comprehensive synthesis of SUDEP risk factors. However, some of our study's limitations include the methodological heterogeneity of the included studies, especially in terms of operational definitions of SUDEP and small sample sizes, thus affecting the generalizability of the results. There is also a lack of prospective studies, which limits the ability to infer causality.

These findings have important implications for clinical practice and research. In clinical practice, they highlight the need for more effective monitoring strategies, including promoting the use of night time monitoring devices and improving the adherence to antiepileptic treatment. In research and development, it is crucial to design large-scale prospective studies that explore the interaction between genetic, cardiac and respiratory factors, as well as the impact of preventive interventions such as educational programs designed for patients and caregivers.

Conclusions

This review highlights SUDEP´s multifactoriality, being GTCS and adherence to treatment as key factors. SUDEP prevention requires a multidisciplinary approach that combines pharmacological treatment optimization, personalized monitoring strategies and major awareness between patients and health professionals. Further studies should approach and solve knowledge gaps to improve the prediction and prevention of this deadly outcome.

References:

1. Tomson T, Walczak T, Sillanpaa M, Sander JWAS (2005) Sudden Unexpected Death in Epilepsy: A Review of Incidence and Risk Factors. Epilepsia 46: 54-61.
2. DeGiorgio CM, Curtis A, Hertling D, Moseley BD (2018) Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention. Acta Neurol Scand 11: 13049.
3. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T (2020) Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology 94.
4. (2019) Biallelic variants in LARS2 and KARS cause deafness and (ovario)leukodystrophy. Neurology 93: 982-982.
5. Baysal Kirac L, Serbest NG, Şahin E, Dede HO, Gurses C, et al. (2017) Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav 71: 60-4.
6. Walczak TS, Leppik IE, D Amelio M, Rarick J, So E, et al. (2001) Incidence and risk factors in sudden unexpected death in epilepsy: A prospective cohort study. Neurology 56: 519-525.
7. Barguilla A, Panadésde Oliveira L, Principe A, Rocamora R (2021) SUDEP-3: probable improvement in risk stratification for sudden death in epilepsy. Epilepsia 62: 2568.
8. Jain P, Nomie K, Kotlov N, Segodin V, Hill H, et al. (2023) Immune depleted tumor microenvironment is associated with poor outcomes and BTK inhibitor resistance in mantle cell lymphoma. Blood Cancer J 13: 1-5.
9. Autio M, Leivonen SK, Bruck O, Mustjoki S, Mészáros Jorgensen J, et al. (2021) Immune cell constitution in the tumor microenvironment predicts the outcome in diffuse large Bcell lymphoma. Haematologica 106: 718-729.
10. Menter T, Tzankov A, Zucca E, Kimby E, Hultdin M, et al. (2020) Prognostic implications of the microenvironment for follicular lymphoma under immunomodulation therapy Br J Haematol 189: 707-717.
11. Zhong W, Liu X, Zhu Z, Li Q, Li K (2021) High levels of Tim-3+Foxp3+Treg cells in the tumor microenvironment is a prognostic indicator of poor survival of diffuse large B cell lymphoma patients. Int Immunopharmacol 96: 107662.
12. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, et al. (2013) Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 54: 1613-1620.
13. Opeskin K, Berkovic SF (2003) Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Seizure12: 456-464.

14. Billakota S, Odom N, Westwood AJ, Hanna E, Pack AM, (2018) Sleep-disordered breathing, neuroendocrine function, and clinical SUDEP risk in patients with epilepsy. Epilepsy Behav EB 87: 78-82.
15. Strzelczyk A, Zschebek G, Bauer S, Baumgartner C, Grond M, et al. (2016) Predictors of and attitudes toward counseling about SUDEP and other epilepsy risk factors among Austrian, German, and Swiss neurologists and neuropediatricians. Epilepsia 57: 612-620.
16. Tellez Zenteno JF, Ronquillo LH, Wiebe S (2005) Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy Res 65: 101-115.
17. Esen Melez I, Arslan MN, Melez DO, Şanli AN, Koç S (2017) Sudden Unexpected Death in Epilepsy: A Retrospective Autopsy Study of 112 Epileptic Patients. Arch Neuropsychiatry 54: 225-233.
18. Langan Y, Nashef L, Sander JW (2005) Case-control study of SUDEP. Neurology 64:1131-1133.
19. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, et al. (2012) Do antiepileptic drugs or generalized tonic–clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 53: 249-252.
20. Maguire MJ, Jackson CF, Marson AG, Nevitt SJ (2020) Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Epilepsy Group, editor. Cochrane Database Syst Rev http://doi.wiley.com/10.1002/14651858.CD011792.pub3.
21. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T (2020) Pharmacologic treatment and SUDEP risk: A nationwide, population-based, case-control study. Neurology 95: e2509-2518.
22. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, et al. (2011) Combined analysis of risk factors for SUDEP. Epilepsia 52: 1150-1159.
23. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ (2007) Sudden unexpected death in epilepsy: a search for risk factors. Epilepsy Behav EB 10: 138-141.
24. Lear Kaul KC, Coughlin L, Dobersen MJ (2005) Sudden unexpected death in epilepsy: a retrospective study. Am J Forensic Med Pathol 26: 11-7.
25. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T (1999) Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet Lond Engl 353: 888-893.
26. Aurlien D, Larsen JP, Gjerstad L, Taubøll E (2012) Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case control study. Epilepsia 53: 258-266.
27. Kloster R, Engelskjon T (1999) Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. J Neurol Neurosurg Psychiatry 67: 439-444.
28. Shankar R, Walker M, McLean B, Laugharne R, Ferrand F, et al. (2016) Steps to prevent SUDEP: the validity of risk factors in the SUDEP and seizure safety checklist: a case control study. J Neurol 263: 1840-1846.
29. Zhang WW, Si Y, Chen T, Chen D, Liu L, et al. (2016) Risks of probable SUDEP among people with convulsive epilepsy in rural West China. Seizure 39: 19-23.
30. Walczak TS, Leppik IE, DAmelio M, Rarick J, So E, et al. (2001) Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 56: 519-525.
31. DeGiorgio CM, Curtis A, Hertling D, Moseley BD (2019) Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention. Acta Neurol Scand 139: 220-230.
32. O Neal TB, Shrestha S, Singh H, Osagie I, Ben Okafor K, et al. (2022) Sudden Unexpected Death in Epilepsy. Neurol Int 14: 600-613.
33. Whitney R, Donner EJ (2019) Risk Factors for Sudden Unexpected Death in Epilepsy (SUDEP) and Their Mitigation. Curr Treat Options Neurol 21: 7.
34. Shorvon S (1997) Risk factors for sudden unexpected death in epilepsy. Epilepsia 38: S20-22.
35. (2024) Plötzlicher unerwarteter Tod bei Epilepsie (SUDEP) Sudden unexpected death in epilepsy (SUDEP): Epidemiologie, kardiale und andere RisikofaktorenEpidemiology, cardiac and other risk factors https://www.researchgate.net/publication/335643757_Plotzlicher_unerwarteter_Tod_bei_Epilepsie_SUDEPSudden_unexpected_death_in_epilepsy_SUDEP_Epidemiologie_kardiale_und_andere_RisikofaktorenEpidemiology_cardiac_and_other_risk_factors.
36. Langan Y (2000) Sudden unexpected death in epilepsy (SUDEP): risk factors and case control studies. Seizure 9:179-183.