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SUDEP in the North American SUDEP Registry
The full spectrum of epilepsies

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Abstract

Objective
To obtain medical records, family interviews, and death-related reports of sudden unexpected
death in epilepsy (SUDEP) cases to better understand SUDEP.

Methods
All cases referred to the North American SUDEP Registry (NASR) between October 2011 and
June 2018 were reviewed; cause of death was determined by consensus review. Available
medical records, death scene investigation reports, autopsy reports, and next-of-kin interviews
were reviewed for all cases of SUDEP. Seizure type, EEG, MRI, and SUDEP classification were
adjudicated by 2 epileptologists.

Results
There were 237 definite and probable cases of SUDEP among 530 NASR participants. SUDEP
decedents had a median age of 26 (range 1–70) years at death, and 38% were female. In 143
with sufficient information, 40% had generalized and 60% had focal epilepsy. SUDEP affected
the full spectrum of epilepsies, from benign epilepsy with centrotemporal spikes (n = 3, 1%) to
intractable epileptic encephalopathies (n = 27, 11%). Most (93%) SUDEPs were unwitnessed;
70% occurred during apparent sleep; and 69% of patients were prone. Only 37% of cases of
SUDEP took their last dose of antiseizure medications (ASMs). Reported lifetime generalized
tonic-clonic seizures (GTCS) were <10 in 33% and 0 in 4%.

Conclusions
NASR participants commonly have clinical features that have been previously been associated
with SUDEP risk such as young adult age, ASM nonadherence, and frequent GTCS. However,
a sizeable minority of SUDEP occurred in patients thought to be treatment responsive or to
have benign epilepsies. These results emphasize the importance of SUDEP education across the
spectrum of epilepsy severities. We aim to make NASR data and biospecimens available for
researchers to advance SUDEP understanding and prevention.

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Glossary

ASM = antiseizure medication; **CPR** = cardiopulmonary resuscitation; **GTCS** = generalized tonic-clonic seizures; **IQR** = interquartile range; **NASR** = North American SUDEP Registry; **NOK** = next of kin; **PNES** = psychogenic nonepileptic seizures; **PWE** = people with epilepsy; **SUDEP** = sudden unexpected death in epilepsy; **VNS** = vagus nerve stimulator.

Sudden unexpected death in epilepsy (SUDEP) is a common cause of death among people with epilepsy (PWE),[1] claiming 1% of patients' lives per decade,[2] and is the second leading neurologic cause of lost potential life-years.[3] When witnessed outside the hospital or recorded on video EEG, most SUDEPs follow ≥1 generalized tonic-clonic seizures (GTCS) with death during the postictal state; however, some SUDEPs occur without a preceding electrographic or clinical seizure.[4,5] Individual risk varies substantially and is highest in those with treatment-resistant epilepsy who have recent and frequent GTCS, especially during sleep.[6] Other risk factors include lack of observation or monitoring in sleep and nonadherence to antiseizure medication (ASM).[7] However, SUDEP can occur in patients with recent onset of epilepsy, well-controlled epilepsy, or benign epilepsies.[8] Parallel cause of death in patients with provoked seizures (e.g., febrile seizures) is not diagnosed as epilepsy; thus, deaths are not SUDEP by definition.[9,10]

Knowledge about the epidemiology, risk factors, mechanisms, and prevention of SUDEP comes from population-based studies, medical examiner office case-control series, and clinical case-control series focused on specific subgroups (e.g., ASM trials, epilepsy surgery, vagus nerve stimulator [VNS], or responsive brain stimulation), epilepsy monitoring unit studies of seizures and postictal states, and animal models.[11–14] These studies have greatly advanced our understanding about SUDEP, yet detailed clinical and pathologic studies remain limited to small samples, often derived from single subgroups (e.g., epilepsy surgery, children, pregnancy, epilepsy monitoring unit) or geographic regions.[4,13,15–20] Larger series often focused on selected features (e.g., nocturnal, witnessed, prone position) or had limited access to detailed clinical data (e.g., medical examiner or VNS series).[21–26]

The North American SUDEP Registry (NASR) is a repository of medical records, comprehensive interviews with family members, and biospecimens (e.g., DNA, brain tissue) to aid investigations of SUDEP pathophysiology. Here, we report the comprehensive study of clinical characteristics and postmortem findings in a large consecutive series of SUDEPs.

Methods

Participants

Since October 2011, NASR has enrolled decedents with epilepsy, living controls with epilepsy, living first-degree relatives of presumed SUDEP cases, and control decedents with or without epilepsy. We reviewed all enrolled cases through June 2018. Family members of the decedents were referred to NASR from physicians, medical examiners or coroners, or advocacy groups (e.g., NIH Center for SUDEP Research, Epilepsy Foundation/SUDEP Institute, Dravet Syndrome Foundation, Dup15q Alliance, Danny Did Foundation) or were self-referred via an online search, recorded at the time of enrollment. If a first-degree relative indicated interest in NASR participation, saliva was collected; if the family member also had epilepsy, medical records were collected, and the case was enrolled as a living control and/or prospective brain donor, according to the individual's wishes.

Standard protocol approvals, registrations, and patient consents

All next of kin (NOK) provided written informed consent, and this study was approved by the New York University Langone Medical Center Institutional Review Board.

Data collection

A research assistant conducted a structured telephone interview that included social/familial history, medication history and adherence, seizure history and semiology, and circumstances of death (data available from Dryad, doi.org/10.5061/dryad.gn74mt3). For 2 cases for whom a language barrier limited verbal interview, NOK completed a questionnaire with assistance from the decedent's physician. Medical records included reports and original data for brain MRIs, EEGs or video EEGs, and ECGs. Seizure types, epilepsy etiology, MRI findings, and EEG results were abstracted with the use of the NIH Common Data Elements for epilepsy.[27] A NASR neurologist or cardiologist adjudicated seizure types, epilepsy syndrome, and diagnostic test findings (EEG/video EEG, MRI, ECG) to confirm diagnosis.

To assess intellectual disability when formal testing was unavailable, we assumed normal intellectual function (IQ > 70) if the individual was not diagnosed with intellectual disability and either ≥12 years of education or full-time employment. Otherwise, intellectual status was considered unknown.

Sleep deprivation during the 24 hours before death was determined through NOK interview or death investigator records, including the decedent self-reporting being exhausted/very tired before terminal sleep, decedent went to sleep late or woke up early, or circadian rhythm disrupted from recent travel (e.g., 1 such case was noted "texting until 12:10 AM and woke up early for work"). Many cases lacked information on sleep status.

SUDEP adjudication

We adjudicated cases using standard SUDEP criteria[1] to determine whether the death was SUDEP: a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death, occurring in benign circumstances in a PWE, with or without evidence for a seizure, excluding documented status epilepticus (seizure duration >30 minutes or seizures without recovery in between). Definite SUDEP met all criteria with complete postmortem examination that did not reveal an alternative cause of death. Definite plus SUDEP met the definite criteria with a health condition or autopsy/toxicologic finding that could have contributed to death. Probable SUDEP met the criteria for definite SUDEP without postmortem examination. Possible SUDEP had a competing cause of death. Two epileptologists (O.D. and D.F.) with SUDEP expertise independently reviewed all records to confirm epilepsy diagnosis and to determine SUDEP classification. In cases with disagreement, a third epileptologist with SUDEP expertise (E.D.) reviewed the case and achieved consensus. Non-SUDEP, near SUDEP, and possible SUDEP deaths were excluded from this analysis.

Statistical analysis

We report mean ± SD or median and interquartile range (IQR) for continuous data. Statistics were performed with IBM SPSS Statistics, version 23 (IBM Corp, Armonk, NY). We assessed differences between SUDEP incidence by days of the week, months, or seasons using a χ^2 goodness-of-fit test.

Data availability

Deidentified data will be available on request to any qualified researcher.

Results

NASR enrolled 331 epilepsy decedents, with 264 definite/plus/probable SUDEPs: definite (n = 135), definite plus (n = 25), probable (n = 77), possible (n = 16), or near (n = 11) cases. We enrolled 56 PWE who died of non-SUDEP causes, and 11 cases had insufficient information to categorize. Here, we report 237 cases of definite (57%), definite plus (11%), and probable SUDEPs (32%). Interviews were conducted in 163 of 237 (69%) cases. In the remainder, history was obtained exclusively from medical records and medical examiner reports.

One additional case was excluded because the individual had no lifetime history of seizures, but the death scene was typical of SUDEP (found in morning dead after period of sleep deprivation, "tangled in comforter on the floor" with arms close to chest with hand in fisted position). Neuropathology revealed focal cortical dysplasia.

Demographics

The median age of the 237 cases of SUDEP was 26 years (range 1–70 years) (figure 1A), and 38% (n = 89) were female. The average age for definite SUDEP cases was 25 years

Figure 1 Distribution of ages, most recent seizures before death, and lifetime seizure frequencies
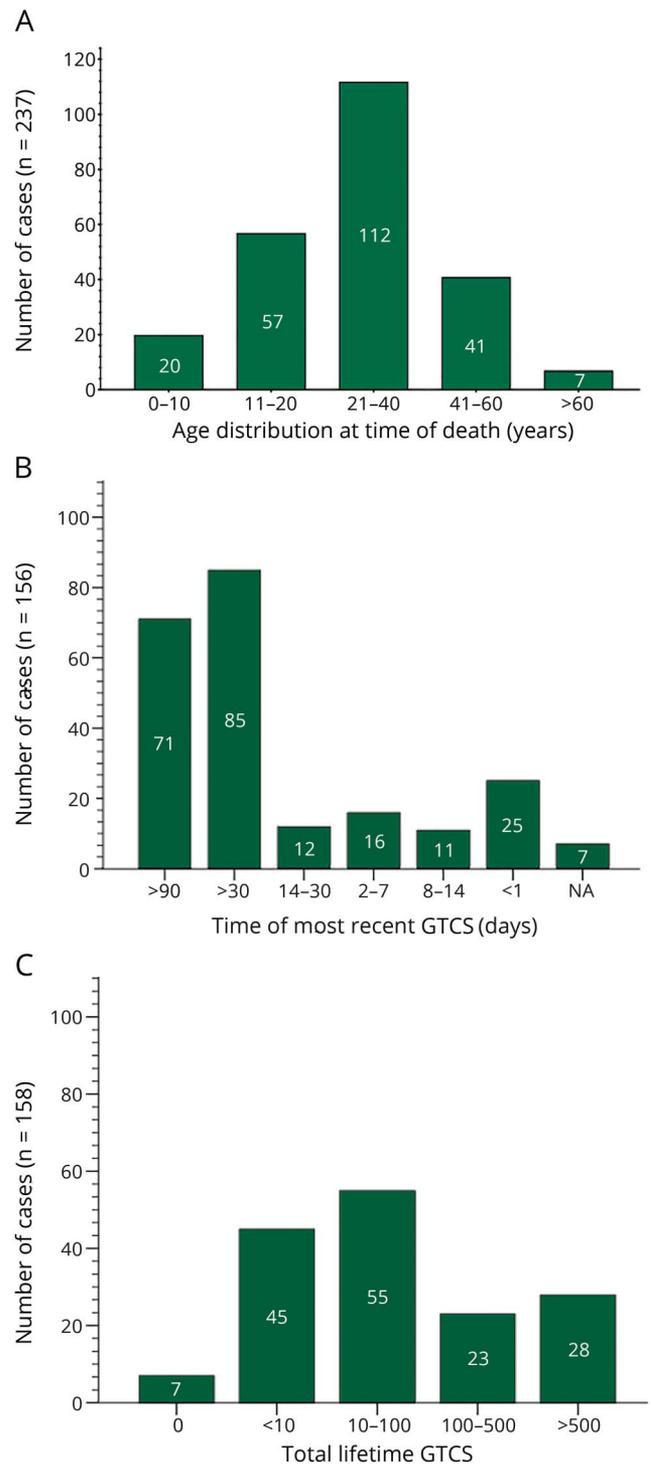
(A) Age distribution at the time of death, (B) time of most recent generalized tonic-clonic seizures (GTCS), and (C) total lifetime GTCS.

(SD 13 years); for definite SUDEP plus, 40 years (SD 14 years); and for probable SUDEP, 24 years (SD 15 years). Ethnicities (reported by NOK interview or listed in medical records) were as follows: white 79% (n = 188), black 9% (n = 22), and Hispanic 11% (n = 25). Other ethnicities (1%)

included South Asian or East Asian American and Native Hawaiian or Pacific Islander. Among 173 adults (age >16 years), education history was available in 140 cases: 26% (37 of 140) had a bachelor's degree or higher; 62% (87 of 140) had some college education; and 88% (123 of 140) had a high school diploma, general equivalency diploma, or greater.

Contact was initiated to NASR by the decedent's NOK through medical examiners (31%, n = 49), patient/family support group (18%, n = 29), the decedent's physician (21%, n = 33), or web search (17%, n = 26). The rest found NASR through other families or physicians (7%, n = 11) or other sources (n = 9), and contact was unspecified in 80 cases. Only 16% (n = 39) of NOK had heard about SUDEP before their relatives' death.

Circumstances of death

Death was witnessed in 7% (16 of 237) of SUDEPs, with a seizure observed immediately preceding death in 10 of 16 (63%) witnessed cases. Of the 6 witnessed cases without terminal seizure, 4 had difficulty breathing immediately before death, and 1 was in a typical postictal state. Thirteen (81%) cases received cardiopulmonary resuscitation (CPR) either by a CPR-trained bystander or directly by EMS personnel. Of 16 witnessed SUDEPs, 7 were presumed asleep and 9 were awake (e.g., exiting the shower, speaking with friends in their room, or sitting on the porch drinking beer).

Many unwitnessed SUDEPs were administered CPR on discovery. Although time between terminal seizure or death and EMS response cannot be determined, it appears that most cases of unwitnessed SUDEP were administered CPR after the decedent had already been discovered dead (table 1).

Only 37% (66 of 180) had reportedly taken their last prescribed ASM dose before death, and 23 cases were not prescribed ASMs.

Of the 157 decedents with narratives surrounding the circumstances of death, 15% (24 of 157) were reported to be sleep deprived at the time of death. The 80 cases (36%) without interviews lacked information to determine sleep status before death.

A full autopsy was performed in 65% (155) of cases (table 1). Of these 155 cases with autopsy, 142 (92%) listed a seizure-related cause or contributing cause of death. The other 13 were attributed to cardiac (9), respiratory (3), or hepatic (1) causes; 6 of these cases were classified as definite plus SUDEP. Brain tissue (whole brain, portions, or slides) was donated for 120 decedents; DNA samples were donated for 144 decedents. Medical examiner death scene investigation reports and autopsy/toxicology reports were obtained for 155 cases (table 2). Full neuropathology examinations were performed by NASR for

Table 1 Circumstances of death (n = 237)

Circumstance of death	n	N	%
Took last ASM dose?	66	180	37
Asleep at time of death	118	168	70
Known recent illness	30	175	17
Room sharing during sleep	57	161	35
CPR performed	108	212	51
Sleep deprived	24	157	15
Full autopsy performed	155	237	65
Found in prone position	128	186	69
Evidence of preceding seizure	123	167	74

Abbreviations: ASM = antiseizure medication; CPR = cardiopulmonary resuscitation.

Table 2 Major autopsy findings (n = 237)

Death report finding	n	%
BMI (n = 166), kg/m^2		
<18	17	10
18.1–25	68	41
25.1–30	44	27
>30.1	37	22
Evidence of preceding seizure (n = 237)		
None	44	19
Incontinence	31	13
Tongue bite	31	13
Blood on pillow	24	10
Bedding askew	6	3
Cardiac autopsy findings (n = 145)		
Atherosclerosis	31	21
Stenosis (coronary artery)	17	12
Hypertrophy	14	10
Pulmonary findings (n = 142)		
Congestion	78	55
Edema	57	40
Neuropathologic findings (n = 130)		
Sclerosis	10	8
Gliosis	8	6
Focal cortical dysplasia	7	5
Hemorrhage	7	5
Congestion/edema	6	5

Abbreviation: BMI = body mass index.

28 decedents; 25 (89%) demonstrated epilepsy-related changes, most commonly gliosis (43%), focal dysgenesis of the dentate gyrus (29%), and focal cortical dysplasias type I/IIA (21%/18%). In 136 cases, the median brain weight was 1,424 g (IQR 1,269–1,542 g). The mean weights of SUDEP brains for both adult women >16 years of age (1,324 g [SD 139 g]) and adult men >16 years of age (1,543 g [SD 201 g]) in our cohort were slightly higher than reported in aggregated autopsy reports of normal brain weights for women (1,287 g) and men (1,418 g).[28] Lung pathology revealed pulmonary edema in 40% (57 of 142) and pulmonary congestion in 55% (78 of 142); congestion and edema concurred in 30% (42) of cases. Genetic analysis of NASR biospecimens for relevant neurologic, cardiac, and respiratory findings is currently being conducted.

Seizure history

Among SUDEPs, the median epilepsy duration was 13 years (available for 198 of 237, IQR 5–23 years). The median age at onset was 10 years (198 of 237, IQR 3–17 years). For the 143 cases with sufficient data to make electroclinical diagnoses, 40% (57) had generalized epilepsy, 60% (86) had focal epilepsy, and 10% (15) had both generalized and focal epilepsies. The remaining 40% (94 of 237) were unclassified due to lack of data, ambiguity, or discordant data (table 3).

The interval between last seizure and SUDEP is plotted in figure 1B. Seven cases had no known lifetime GTCS (5 had focal unaware seizures and 2 had focal seizures with preserved awareness). Estimated lifetime number of GTCS is

Table 3 Seizure histories in cases of SUDEP with sufficient information to adjudicate (143 of 237)

Seizure history	n	N	%
Generalized	57	143	40
Tonic-clonic	46	143	32
Focal	86	143	60
Focal to bilateral	67	143	47
Preserved awareness	20	143	14
Impaired awareness	59	143	41
Unclassified	94	237	40
Both	15	143	10
Seizure-free at time of death[a]	27	182	15
Psychogenic seizures	6	166	4

	Median		IQR
Duration, y	12		5–23
Age at onset, y	10		3–17

Abbreviations: IQR = interquartile range; SUDEP = sudden unexpected death in epilepsy.
[a] Seizure-free at time of death includes only cases who have experienced a period of seizure freedom in the full year before death, excluding possible terminal seizure.

summarized in figure 1C. Of the 28 cases whose family members reported >500 lifetime GTCS, 4 had Lennox-Gastaut syndrome, 7 had Dup15q chromosomal abnormality, 6 had Dravet syndrome, and 1 had both Lennox-Gastaut syndrome and Dup15q.

Data on seizure frequency before death were obtained from interviews and medical records and represent best estimates for many patients. In the month before death, 54% had no GTCS. During the 3 months before death in the 153 patients with data available, 42% had no GTCS and 14% had 1 GTCS. In 182 cases with sufficient data in the year before death, 15% were seizure-free.

Among the 27 patients who were seizure-free during the year before death, 7 had idiopathic generalized epilepsy (4 with GTCS), 9 had focal epilepsy (5 with GTCS), and 11 had unknown epilepsy classification. The average age at death for cases seizure-free in the year before death was 29 years, and 63% were male, similar to the overall cohort. Among these 27 cases, 82% were taking ASMs, and 8% had undergone epilepsy surgery or VNS implantation.

Psychogenic nonepileptic seizures (PNES) with comorbid epilepsy were diagnosed in 6 of 166 (4%) SUDEPs; 4 were male. For the 6 cases of PNES, the median age at epilepsy diagnosis for the group was 4.5 years (IQR 0.9–10.25 years), and the median age at PNES diagnosis for the group was 25 years (n = 6). The median age at death for the PNES group was 22 years (IQR 12.75–30.5 years), lower than for the SUDEP cases without PNES: median age at epilepsy diagnosis was 10 years (IQR 3.0–17.0 years) and at death was 26 years (IQR 18.0–47.0 years).

Epilepsy treatment history

Among the 203 cases with sufficient data, 89% (n = 180) were prescribed ASMs, and 23 (11%) were never prescribed an ASM. During interviews, NOK recalled ASM adherence status in 170 cases, even when specific ASMs could not be named; of these, 66% (113) were adherent and 34% were nonadherent (frequently forgot ASMs, took subtherapeutic doses to reduce side effects, or intentionally skipped or stopped ASM). Medication adherence was unknown in 44 cases.

Data on specific ASMs at the time of death were available in 180 of 237 cases, compiled from postmortem testing, medical records, and recall during the interview. The most frequent ASMs were levetiracetam (39%, n = 71), lamotrigine (26%, n = 47), valproate (15%, n = 27), topiramate (13%, n = 24), and oxcarbazepine (12%, n = 22). For these 180 cases, 56 were taking 1 ASM, 62 were taking 2 ASMs, and 62 were taking ≥3 ASM (2 cases were taking 6 concurrent ASMs). Of the 140 cases with toxicology reports, no antiepileptic drugs were detected in 40 (29%), including patients who were nonadherent (34) and those who were never prescribed antiepileptic drugs (6).

Of 57 patients who were nonadherent with ASMs, information about psychiatric history was obtained in 47: 70% had no psychiatric conditions listed and 30% had anxiety disorder (n = 8), bipolar disorder (n = 2) schizophrenia (n = 2), adjustment disorder (n = 1), or extreme anger (n = 1). Of these nonadherent cases, 26 were active alcohol users, and 19 were currently using recreational drugs. The mean age at death for these cases was 28 years, similar to the group as a whole.

Epilepsy surgery was performed on 18% (42 of 237) of cases, including temporal lobectomies (n = 19), extratemporal lobe resections (n = 3), corpus callosotomy (n = 6), and lesionectomy (n = 8) (arteriovenous malformation [n = 2], tumor [n = 2], ganglioma [n = 1], or subdural and epidural hematoma [n = 1], and 1 foreign body excision). Neurostimulating devices were implanted in 32 of 237 (14%): 31 had a VNS, and 1 had a deep brain stimulator.

Dietary therapy for epilepsy was attempted by 25 of 237 (11%): ketogenic diet (n = 20), modified Atkins diet (n = 4), low glycemic diet (n = 2), or other seizure diets (n = 3), with some attempting >1 therapeutic diet in their lifetime.

Medical and psychiatric comorbid conditions are summarized in figure 2.

Epilepsy syndromes and etiologies

Epilepsy syndromes included Dravet syndrome in 5% (n = 13), juvenile myoclonic epilepsy in 4% (n = 9), Dup15q chromosomal abnormality in 4% (n = 9), febrile seizure plus syndrome in 3% (n = 7), Lennox-Gastaut syndrome in 3% (n = 5), and benign epilepsy with centrotemporal spikes in 1% (n = 3).[8] The causes of epilepsy for SUDEP cases were often unknown. Among 150 cases with sufficient data to classify etiology, 43% (64) had epilepsy of unknown cause. The rest

included genetic/presumed genetic or epileptic encephalopathies (n = 33), traumatic brain injury (n = 11), malformations of cortical development (n = 7), or a viral, bacterial, or parasitic infection (n = 4).

MRI, EEG, ECG findings are listed in table 4.

Other common risk factors

Around the time of death, 15 had alcohol use disorder; of these, 4 were drinking alcohol the night they died, with 3 of 4 binge drinking that night. In most cases, data were not available on alcohol consumption on the day before death. Toxicology reports from 140 decedents found alcohol in 6%, although this may be an overestimate due to postmortem decomposition artifact and may be an underestimate of the role of alcohol withdrawal, which may be associated with nondetectable ethanol levels.

History of recreational drug use was assessed in 196 cases: 12% used illegal drugs near the time of death, and 7% used them previously. These drugs included marijuana (n = 33), amphetamines (n = 4), cocaine (n = 2), and heroin (n = 2). No lifetime use of illicit drugs was reported in 81%. Among medical examiner–referred cases (n = 49), 20% had used illegal drugs and 12% used illicit drugs at the time of death. Toxicology reports in 140 cases found illegal drugs (10%), including marijuana (n = 9), amphetamines (n = 4), and opiates (n = 1).

One hundred seventy-six cases shared the bed while sleeping, most frequently with spouses or parents. Among the 118 cases with data, 86% (n = 102) had an estimated IQ >70, while 14% (n = 16) had an IQ <70.

There was no relationship between SUDEP and day of the week ($\chi^2 = 2.013$, $p < 0.05$) (n = 230), month of year ($\chi^2 =$

Figure 2 Comorbid conditions reported in cases of sudden unexpected death in epilepsy (n = 237)
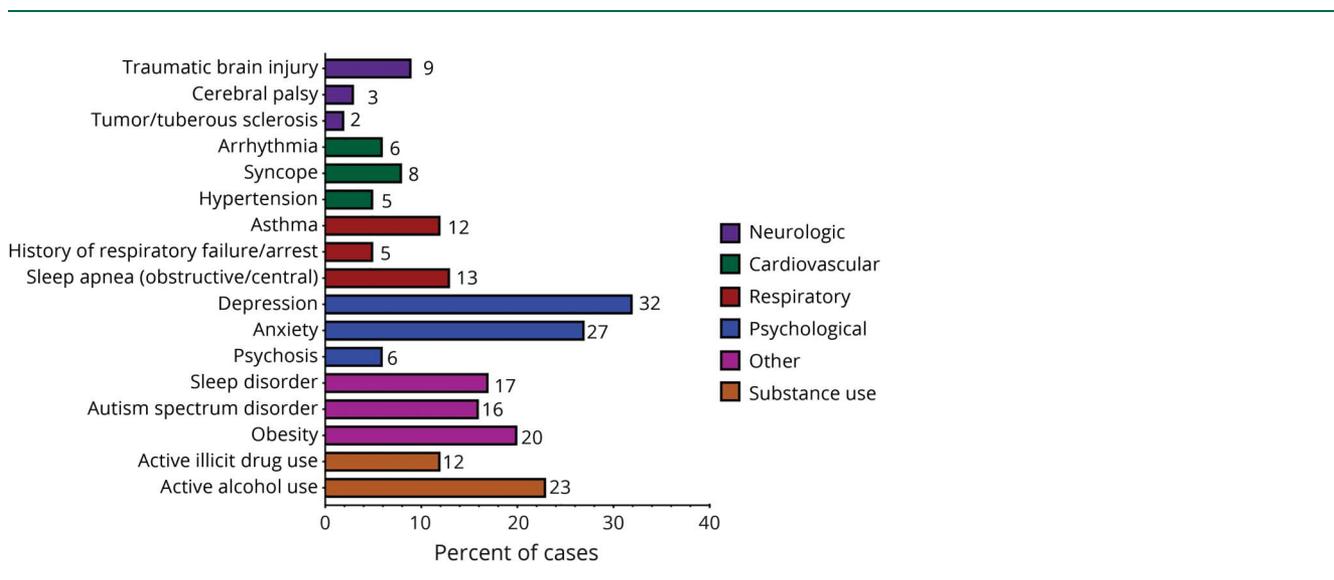
Table 4 EEG, MRI, and ECG findings

Finding	n	%
EEG (n = 129)		
Normal	22	17
Focal slowing	15 L/14 R	12 L/11 R
Focal dysfunction/dysrhythmia	13 L/22 R	10 L/17 R
Generalized slowing	40	31
Epileptiform activity	36	28
Generalized dysfunction/dysrhythmia	32	25
Seizure recorded	45	35
MRI (n = 106)		
Normal	60	57
Postoperative/resection changes	14	13
Atrophy	10	9
Sclerosis (any)	9	8
Mesial temporal sclerosis	9	8
Cyst	5	5
Dysplasia	3	3
Tumor/lesion	2	2
ECG (n = 47)		
Normal	18	38
Tachycardia	8	17
Arrhythmia (+LQTS)	7	15
Atrial enlargement	4	9

Abbreviation: LQTS = long-QT syndrome.

2.82, $p < 0.05$) (n = 230), or season ($\chi^2 = 0.5165$, $p < 0.05$) (n = 230).

Discussion

We report 237 cases of definite and probable SUDEP, the largest series with extensive ascertainment and adjudication of medical records, death scene investigations, and autopsy reports to confirm epilepsy diagnosis and to accurately identify seizure types and epilepsy syndromes; EEG, MRI, and ECG findings; and SUDEP classification. Our data expand what is currently considered the typical case or spectrum of SUDEP. Although SUDEP is most common in the intractable epilepsies, our findings establish that SUDEP affects the full spectrum of epilepsies, from benign epilepsy with centrotemporal spikes to epileptic encephalopathies and failed resective surgeries. The distribution of generalized and focal epilepsy paralleled their frequency in the general epilepsy population: 40% had generalized seizures, 60% had focal

seizures, and 10% had both.[29,30] Finally, lack of ASMs was common: 11% were not prescribed ASMs, with only 37% of those prescribed ASMs reported to have taken their last dose before death. This suggests that a single missed dose of ASM may, in some patients and circumstances, increase SUDEP risk.

Because SUDEP can occur in patients with epilepsy who are seizure-free, have never had tonic-clonic seizure, or were diagnosed with a benign epilepsy syndrome, clinicians should discuss SUDEP with all PWE for 2 reasons. First, some reassurance can be given to relieve anxiety for those at low risk (e.g., focal aware or absence seizures only). Second and most important, patients and families must understand the critical—and potentially lifesaving—importance of seizure control. Many SUDEPs could likely be prevented by ASM adherence and lifestyle factors (sleep hygiene, limited/no alcohol), and many lives are likely saved by patients and families pursuing aggressive seizure management and possibly by monitoring to detect seizures and provide prompt first aid.

Our series paralleled prior studies, with the peak age distribution in young adults, frequent occurrence in apparent sleep (70%), death in the prone position (69%), low rate of witnessed death (7%), and evidence of a preceding seizure in most cases (74%).[21,31] However, 27% of our sample was <16 years of age, which is 2-fold more than the combined 13% of SUDEPs in the 0- to 20-year age ranges reported in a pooled analysis from high-quality population-based studies of SUDEP incidence across all age groups.[2] Our findings, although partly reflecting referral bias, accord with recent population-based cohorts showing that pediatric SUDEPs are more common than suspected.[2,32] SUDEPs in older children and young adults (11–40 years of age, 71%), unwitnessed or unaccompanied death (93%), and found in the prone position (69%) were prevalent in our study, all of which are previously documented SUDEP risk factors.[9]

Among the 16 (7%) witnessed SUDEPs, 10 had seizures immediately preceding death. Of the 6 other cases without preceding seizure, 4 had difficulty breathing around the terminal event. This provides further anecdotal evidence for proposed pathophysiologic mechanisms of SUDEP of seizures followed by acute respiratory distress or arrest.[33] We need additional studies of cases of witnessed near SUDEP in the epilepsy monitoring unit with cardiopulmonary monitoring devices. Access to rapidly responsive emergency medical providers was key in resuscitating cases for >1 hour (i.e., near SUDEP)[34] and, in many cases, preventing death.

Among unwitnessed cases of SUDEP with known sleep state at the time of death (153), death was more likely to occur during sleep (73%) than while awake (27%). This contrasts to cases of witnessed SUDEP (16), which were more frequently awake (55%) than asleep. Witnessed seizures are more likely to receive rapid, potentially lifesaving first aid, which would reduce the frequency of witnessed SUDEPs. Sleep state may

be conducive to SUDEP independently of a witness or first aid. For some, a perfect storm of sleep state, altered reduced sympathetic activity, serotonin circadian cycling, and more prolonged postictal generalized EEG suppression leading to cerebral shutdown may combine to impair autonomic function, arousal, and respiration, making SUDEP more likely with seizures during sleep.[35,36]

As with prior studies, we found that recent history and high frequency of GTCS are common among SUDEP decedents. The high number of lifetime GTCS in this cohort partly reflects patients with epileptic encephalopathies for which very frequent GTCS are retrospectively reported by parents.[37]

While the majority of decedents in this study had a high lifetime GTCS burden, many reported good seizure control before death. Paradoxically, most SUDEPs in our cohort occurred in patients who are traditionally considered at low SUDEP risk. Our findings also highlight an important issue regarding GTCS frequency and SUDEP. While frequent GTCS are known to increase the relative risk of SUDEP, most PWE have relatively few GTCS. Therefore, in absolute numbers, SUDEP occurs more frequently in people who have relatively milder forms of epilepsy. However, these findings are consistent in that they highlight different aspects of SUDEP: high GTCS frequency increases SUDEP risk in a small group, but the low-risk group is much larger and accounts for most SUDEPs.[12] Long periods of seizure freedom could potentially increase SUDEP risk if seizures that occur after a long period of seizure freedom are more dangerous due to a relative lack of tolerance or adaptive recovery responses. One mother feared long periods of seizure freedom in her daughter because the GTCS that followed would often be worse than her typical convulsions. Relatively seizure-free patients must remain vigilant to mitigate risk because ASM nonadherence or lifestyle lapses could prove fatal.

Seven (3%) cases never had a GTCS before SUDEP. Thus, SUDEP risk is not limited to patients with frequent or uncontrolled GTCS. SUDEP should be discussed with all patients and families, regardless of their seizure type, severity, or frequency.[10]

We studied other SUDEP risk factors, including intellectual disability, alcohol or illicit drug use, and medication nonadherence. The IQ range of our cohort was similar to that of epilepsy populations; 14% had intellectual disability.[19] Alcohol use was not frequent in our cohort; 23% were current alcohol users, and 64% never used alcohol, similar to prior studies.[7] However, our data reflect only available history, and many SUDEP cases were referred by medical examiners and had limited history. Toxicology findings may bias referrals and influence adjudication because deaths with illicit drug use findings are more likely adjudicated as not SUDEP or possible SUDEP (i.e., overdose is a competing cause of death).

At least 15% of decedents were sleep deprived before death. This conservative figure includes only cases for whom this information was explicitly stated by NOK or confirmed through investigative reports. Because sleep deprivation is a seizure provocation factor, it may be a risk factor for SUDEP.[38] We found no relationship of SUDEP to day of the week, month, or season of the year, similar to prior studies.[39]

Only 16% of NOK were aware of SUDEP before their loved one's death, similar to our earlier report[40]; 74% of this group were glad it was discussed. Among those who had not learned of SUDEP, 78% wish they had been told beforehand. Doctors routinely fail to educate patients and families about SUDEP and ways to reduce risk despite families' interest in this information and its potential to save the family member's life.[41]

Our cohort had higher comorbidity rates than the general epilepsy population, including depressive (32% compared to 23% reported in a meta-analysis of psychiatric disorders among PWE[42]) and anxiety disorders (27% compared to 11%–25% in the same reference study[42]), autism spectrum disorder (16%), and apnea (13%). While the high rates of autism spectrum disorder and possibly apnea may reflect our biased recruiting of patients with Dup15q syndrome and Dravet syndrome, high rates of depressive and anxiety disorders exceed that of the general epilepsy population and are biased down by the epileptic encephalopathy populations, in which these psychiatric diagnoses were infrequent. In patients with treatment-resistant epilepsy who underwent epilepsy surgery and had prospective, systematic assessments, moderate to severe depression and anxiety were identified in 22.1% and 24.7%, respectively.[43] In contrast, our data were limited by lack of available medical records, and we lacked either prospective or systematic psychiatric assessments. The prevalence of psychiatric comorbid conditions was likely higher than we identified. A large population-based study in Sweden found that PWE have an ≈11-fold increase in the odds ratio of death during a 55-year follow-up period compared to the general population.[44] Of the 15.8% who died of external causes (e.g., suicide, accident, drowning, assault), psychiatric comorbid conditions, especially depression and substance misuse, occurred in 75%.

Our study has multiple limitations. Self-referral or advocacy group referrals likely biased our sample toward higher socioeconomic, white, and younger cases. Our series comprised cases from various referral sources, with only 31% coming from a population base (i.e., San Diego County). In contrast, in the population-based recruitment through medical examiner office referrals, only 17 of 49 cases had finished high school, and 12% were unemployed. Furthermore, 47% of those enrolled through a medical examiner were black or Hispanic/Latino vs 13% of our cohort referred through other sources. The families of most decedents had high medical literacy or access to healthcare providers to learn of NASR. This highlights the nonrandomness of our missing data, often skewed toward collecting higher-quality medical records from patients of a higher socioeconomic status who had more access to specialty care. Interviews were more frequently

conducted in these cases than in medical examiner referrals, for which NOK often waived consent to be recontacted or were lost to follow-up. In the 31% of our cases without interviews, information relied on investigative reports and medical records, which often have limited data. Thus, data including last witnessed GTCS and medication compliance were inconsistent, limiting the generalizability of conclusions about SUDEP mechanisms. We hypothesize that ASM non-adherence, sleep deprivation, alcohol withdrawal, and comorbid psychiatric disorders may have a greater role in SUDEP than we could identify.

Data were also limited by recall bias, inherent in retrospective interviews. Although we sought family interviews shortly after enrollment, many were postponed due to grieving or difficulty recontacting. This time interval was even longer among cases enrolled months or years after death. Details on circumstances of dying, medication compliance, and seizure phenotype in many cases were ambiguous. Many parents of adult children lacked accurate information about their child's seizure frequency, history of substance abuse, or other details about daily life. Our inability to classify epilepsy syndrome as focal or generalized in 40% of cases reflects inclusion of medical examiner cases who often lacked routine neurologic or other medical care. In other cases, despite care at epilepsy centers, semiologic features (e.g., tonic-clonic seizures without aura) or normal/nonspecific EEG findings did not permit classification.

The lack of a population-based cohort or representative control cohort limits our ability to compare and determine possible risk factors between cases of SUDEP and living cases of epilepsy or non-SUDEP epilepsy deaths. NASR hopes to recruit representative epilepsy and nonepilepsy control cases to compare to cases of SUDEP.

We will make NASR data available to physicians and researchers to collaborate or perform their own historical, genetic, and pathologic analyses. We hope to leverage NASR data and biospecimens to accelerate the understanding the risk factors and mechanisms underlying SUDEP and to advance preventive strategies and interventions. For more information, please see sudepregistry.org.

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Publication history

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Appendix *(continued)*

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Orrin Devinsky, MD	Comprehensive Epilepsy Center New York University School of Medicine, NY	Author, principal investigator	Design and conceptualized study, data collection, drafting and revision

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