FULL-LENGTH ORIGINAL RESEARCH

Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation

Orrin Devinsky1 | Daniel Friedman1 | Robert B Duckrow2 | Nathan B Fountain3 | Ryder P Gwinn4 | James W Leiphart5 | Anthony M Murro6 | Paul C Van Ness7

1NYU Langone Medical Center, New York, NY, USA
2Yale University School of Medicine, New Haven, CT, USA
3University of Virginia, Charlottesville, VA, USA
4Swedish Neuroscience Institute, Seattle, WA, USA
5Inova Medical Group, Mclean, VA, USA
6Augusta University Medical Center, Augusta, GA, USA
7Baylor College of Medicine, Houston, TX, USA

Correspondence
Orrin Devinsky, NYU Langone Medical Center, New York, NY, USA.
Email: od4@nyu.edu

Summary
Objective: To study the incidence and clinical features of sudden unexpected death in epilepsy (SUDEP) in patients treated with direct brain-responsive stimulation with the RNS System.

Methods: All deaths in patients treated in clinical trials (N = 256) or following U.S. Food and Drug Administration (FDA) approval (N = 451) through May 5, 2016, were adjudicated for SUDEP.

Results: There were 14 deaths among 707 patients (2208 postimplantation years), including 2 possible, 1 probable, and 4 definite SUDEP events. The rate of probable or definite SUDEP was 2.0/1000 (95% confidence interval [CI] 0.7-5.2) over 2036 patient stimulation years and 2.3/1000 (95% CI 0.9-5.4) over 2208 patient implant years. Stored electrocorticograms around the time of death were available for 4 patients with probable/definite SUDEP and revealed the following: frequent epileptiform activity ending abruptly (n = 2), no epileptiform activity or seizures (n = 1), and an electrographic and witnessed seizure with cessation of postictal electrocorticography (ECoG) activity associated with apnea and pulselessness (n = 1).

Significance: The SUDEP rate of 2.0/1000 patient stimulation years among patients treated with the RNS System is favorable relative to treatment-resistant epilepsy patients randomized to the placebo arm of add-on drug studies or with seizures after resective surgery. Our findings support that treatments that reduce seizures reduce SUDEP risk and that not all SUDEPs follow seizures.

KEYWORDS
brain stimulation, closed-loop, neuromodulation, partial seizures, sudden unexpected death in epilepsy

1 | INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of epilepsy-related death, with an incidence (per 1000-patient-years) that rises with epilepsy severity: 0.9-2.3 in the community, 3.2-5.9 among treatment-resistant epilepsy (TRE) populations, and 6.3-9.3 among patients considered for epilepsy surgery populations.1,2 Most witnessed SUDEPs have occurred following seizures, especially generalized tonic–clonic seizures (GTCS)2,3 and interventions to reduce seizure frequency and severity are the most effective preventive strategy.4,5

The RNS System (NeuroPace, Mountain View, CA, USA) is a targeted direct brain responsive neurostimulator...
that is approved by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy for adults (≥18 years) with TRE with frequent and disabling partial onset seizures localized to no more than 2 epileptogenic foci.6,7 The neurostimulator detects and stimulates in response to electrocorticographic activity identified by the physician, such as epileptiform activity and electrographic seizures. The time, duration, and location of detections are stored, as are samples of the electrocorticography (ECoG) based on specific types of electrocorticographic detections, prespecified schedules, or patient or caregiver identified clinical events (marked by magnet activation). The RNS System reduces seizure frequency,7 and therefore, like other antiseizure therapies, could reduce SUDEP risk. In addition, because the RNS System can also record objective data on the timing of seizures and seizure-like ECoG, the device can potentially elucidate SUDEP mechanisms by providing electrophysiological signals in the hours prior to death.

2 | METHODS

All patients treated either as part of clinical trials (N = 256) or as part of clinical care following FDA approval (N = 451) through May 5, 2016, were included in the analysis (total N = 707). As part of the clinical trials and postapproval monitoring, all deaths in patients implanted with the RNS System are reported and investigated. In all deaths, efforts are made to retrieve and interrogate the neurostimulator, obtain autopsy reports when available, and review the circumstances surrounding death. All patient deaths are assessed by a SUDEP adjudication committee comprising an epileptologist-epidemiologist, a second epileptologist, and a pathologist-medical examiner who review all available medical and forensic records related to the terminal event. The committee reaches a conclusion, using Annegers criteria, as to whether the death was possibly, probably, or definitely related to SUDEP or was not SUDEP.9 In our analyses, rates of probable and definite SUDEP were calculated according to total implant and stimulation years (time when the device was delivering therapy). SUDEP rates and 95% confidence intervals (CIs) were used. Those deaths determined to be probable or definite SUDEP were included in the analysis. Age-adjusted standardized mortality ratios (SMRs) were calculated based on expected death rates per 10-year age group for the United States using 2007 estimates.9

3 | RESULTS

Demographic data were available for patients studied in the clinical trials (N = 256) and were presented previously.6,7 The mean age was 34 years (range 18-66), duration of epilepsy 19.6 years (range 2-57), and number of antiepileptic drugs (AEDs) being taken 2.9 (range 0-8). The median number of simple partial, complex partial, or GTCS per month was 10.2 (mean 50.7). Vagus nerve stimulation was previously used by 32% of patients, and 34% had undergone epilepsy surgery. Demographic data, other than age, are unavailable for patients treated outside of the clinical trials (N = 451). The mean age of nonstudy patients was 36 years (range 9-75); however, 5 of the 451 patients did not provide date of birth.

There were 14 deaths across the 707 patients with a total of 2208 years of postimplantation follow-up (data cut-off 5/5/2016). Age-adjusted SMR for all-cause mortality was 2.15 (95% CI 1.22-3.52). Causes of death were the following: suicide (n = 2; both had prior depression; 1 was no longer treated with the RNS System), status epilepticus (n = 1; patient had subtherapeutic AED levels), lymphoma (n = 1), colon cancer (n = 1), respiratory failure (n = 1), and aspiration pneumonia (n = 1). There were 2 possible, 1 probable, and 4 definite SUDEP events. The rates of probable or definite SUDEP are shown in Table 1. As of the cut-off date, there have been no additional SUDEP cases in patients who received the device after FDA approval. The rate of probable and definite SUDEP for patients studied in the clinical trials was 2.4 per 1000 patient stimulation years (95% CI 0.9-6.4). For all patients treated with the RNS System (including those first treated after FDA approval), the rate of probable or definite SUDEP was 2.0 per 1000 (95% CI 0.7-5.2) over 2036 patient stimulation years and 2.3 per 1000 (95% CI: 0.9-5.4) over 2208 patient implant years (ie, the latter also includes patients in whom the device was implanted but not enabled for stimulation). Within the 707 patients, the age-adjusted SMR for definite and probable SUDEP was 0.75 (95% CI 0.27-1.65).

Patient characteristics for the 7 possible, probable, or definite SUDEP cases are shown in Table 2. Of these
patients, 3 (Patients 2, 5, and 6) had a greater than 50% reduction in seizures relative to baseline in the final 3 months of life. Five patients had responsive stimulation enabled at the time of death. Two patients had responsive stimulation disabled at the time of death, either to evaluate the effect of responsive stimulation on seizure frequency, or because additional detection information was desired prior to enabling responsive stimulation. Figure 1 summarizes the RNS System data that are available from Patients 2-7 around the time of death. Patient 1 was buried before neurostimulator data could be obtained.

Patient 2 had no detections after the most recent personal contact 5 hours before being found dead. Patient 3 had increased detections and one electrographic seizure in the hour before detections ceased. Patient 4 had increased detections and 3 episodes during which the electrocorticographic activity caused a saturation of the amplifiers (electrographic seizures) in the 3 hours before detections ceased. Figure 1A shows that at approximately 19:00, the number and duration of detected episodes increased. The ECoG at 21:45 triggered by detection of a prolonged episode indicative of an electrographic seizure (Long Episode; Figure 1B4a) was typical of the patient’s clinical seizures and included 3 saturations. Three minutes later, the magnet stored ECoG at 21:48 (Figure 1B4b) showed severe suppression of ECoG activity punctuated by intermittent bursts of activity. A scheduled ECoG stored approximately 6 hours later (Figure 1B4c), after the patient was declared dead, showed electrocerebral silence. Patient 5 had a somewhat increased detection rate, 2 long episodes, and 5 saturations in the 5 hours before detections ceased. Patient 6 had an increased detection rate, increased episode durations, and 6 saturations in the 3 hours before detections ceased. Patient 7 had a decreased detection rate starting 3 hours before death, and shorter detection episodes starting 1 hour before detections ceased.

4 | DISCUSSION

We identified 5 probable or definite SUDEP events among patients implanted with the RNS System. The overall SUDEP rate in this population was 2.0 per 1000 patient years for those actively treated with responsive stimulation. Three of the 5 SUDEP cases had increased epileptiform activity in the hours prior to death. One decedent had both clinical and electrographic evidence of seizures before death, whereas 2 others had increased detections supportive of electrographic seizures but lack of witnessed clinical seizures or stored ECoG precluded confirmation. Notably, 1 subject did not demonstrate any evidence of electrographic seizures or increased epileptiform activity prior to death.

The data obtained from SUDEP decedents treated with the RNS System supports the heterogenous mechanisms of SUDEP. Most SUDEP witnessed in the hospital or in the community follows an observed seizure.2,3 In many unwitnessed cases there is circumstantial evidence of a terminal seizure (tongue bite, etc.).8 However, in a minority of witnessed SUDEP cases there is no clinical seizure prior to death; a recent report described 3 sudden deaths in patients with epilepsy who were undergoing electroencephalography (EEG) monitoring without evidence of a terminal electrographic seizure.10 In all 3 cases, autopsy revealed no structural or toxicological cause of death, and they were classified as definite SUDEP according to Nashef et al. (2012) criteria.8 In this series, 1 SUDEP case also had no electrographic evidence of terminal seizure recorded on the RNS System. Although the patient may have had a seizure arise in a cerebral location not sampled by the device, it was likely that this SUDEP was seizure-independent. Sudden cardiac death due to arrhythmia may be responsible for a minority of SUDEPs. Indeed, a recent series examining whole-exome sequencing in SUDEP cases demonstrated that 7% of decedents had mutations in genes associated with long-QT syndrome,11 a cause of lethal cardiac arrhythmias.

Mortality rates are substantially increased in persons with epilepsy, and SUDEP is a common, although poorly understood, cause of death. SUDEP rates are highest for those with more severe epilepsy. The risk for SUDEP is higher with medically intractable partial onset and secondarily generalized seizures, and in patients with frequent seizures, a long duration of epilepsy, and taking a large number of AEDs.12,13 These clinical risk factors are

TABLE 1 Estimates of definite/probable SUDEP rates for patients implanted with the RNS System during the clinical development program and for all patients implanted

| Category                          | No. of events | Years of data | Estimated rate per 1000 y | 95% CI (lower) | 95% CI (upper) |
|-----------------------------------|---------------|---------------|--------------------------|----------------|----------------|
| SUDEP rates for patients in the RNS System clinical trials (N = 256) |               |               |                          |                |                |
| Implant years                     | 5             | 1774.7        | 2.8                      | 1.2            | 6.8            |
| Stimulation years                 | 4             | 1671.2        | 2.4                      | 0.9            | 6.4            |
| SUDEP rates for all patients treated with the RNS System as of 5/5/2016, including patients from clinical trials and postapproval monitoring (N = 707) |               |               |                          |                |                |
| Implant years                     | 5             | 2208.0        | 2.3                      | 0.9            | 5.4            |
| Stimulation years                 | 4             | 2035.7        | 2.0                      | 0.7            | 5.2            |

557
| Subject no. | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Classification | Definite SUDEP | Definite SUDEP | Definite SUDEP | Definite SUDEP | Probable SUDEP | Possible SUDEP | Possible SUDEP |
| Etiology | Developmental | Cryptogenic | Developmental | Birth trauma | Head trauma, aqueductal stenosis and hydrocephalus | Mesial temporal sclerosis | Mesial temporal sclerosis |
| Seizure onsets | Right frontal parietal | Left mesial temporal | Bilateral frontal | Bilateral mesial temporal | Left mesial temporal | Left mesial temporal | Bilateral mesial temporal |
| Number of foci | 2 | 1 | 2 | 2 | 1 | 1 | 2 |
| Lead locations | 2 Right parietal strips | 1 Hippocampal depth, 1 anteromedial temporal strip | 2 Frontal strips | Bilateral hippocampal depths | 2 Left temporal strips; 1 anterior and 1 posterior | 1 Hippocampal depth, 1 temporal strip | Bilateral hippocampal depths |
| MRI findings | Right temporal atrophy | Nonlesional | Nonlesional | Bilateral mesial temporal sclerosis | Nonlesional | Left mesial temporal sclerosis | Bilateral mesial temporal sclerosis |
| Age at epilepsy onset (years) | 12 | 46 | 3 | 21 | 29 | 3 | 8 |
| Age at RNS implant (years) | 24 | 52 | 21 | 45 | 46 | 29 | 48 |
| Previous surgery for epilepsy | Right parietal topectomy, right temporal resection | No | No | No | No | Right mesial temporal resection | No |
| Prior intracranial monitoring | Yes | Yes | Yes | Yes | Yes | No | No |
| Prior treatment with vagus nerve stimulation | No | Yes | Yes | No | No | Yes | No |
| AEDs at enrolment | Oxcarbazepine zonisamide phenytoin | Oxcarbazepine levetiracetam | Tiagabine lorazepam phenytoin | Pregabalin | Carbamazepine lorazepam | Levetiracetam | Levetiracetam |
| Days implanted | 473 | 856 | 324 | 351 | 1276 | 594 | 36 |
| Days of stimulation | 361 | 459 | 295 | 323 | 1129 | 450 | 0 |
| % Change in seizure frequency (based on most recent 3 mo of seizure diary data) | 0% | −59% | +9% | −6% | −69% | −54% | −44% |
| Baseline GTCS/month | 0.3 | 0.0 | 5.3 | 1.0 | 1.3 | 0.3 | 0.0 |
| Baseline disabling seizures/month | 13.2 | 7.3 | 47.7 | 88.3 | 4.3 | 8.7 | 9.3 |

(Continues)
| Subject no. | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| **RNS System evidence of terminal seizure** | No data on or near DOD | No, last long episode was 2 d prior to death | Yes | Yes | Yes | Yes | Yes |
| | | | ECoG recording of a seizure at 04:23 on DOD | ECoG recording of a seizure at 21:45 on DOD | Long episodes at 01:30, 04:30 on DOD | Long episodes at 15:02, 15:03 on DOD | ECoG at 22:54 on DOD |
| **Responsive stimulation @ time of death** | Enabled | Disabled | Enabled | Enabled | Enabled | Enabled | Disabled |
| **Autopsy findings** | Final report: Moderate cerebral vascular congestion, granulomatous changes in dura and adjacent cortex | Final report: Left frontal cerebral cavernous angioma, diffuse cerebral congestion, hypertensive changes, adrenal cortical adenoma | Final report: No anatomic abnormalities | Final report: Remote right occipital stroke, diffuse cerebral edema, cardiac hypertrophy and arterio nephrosclerosis | Not performed | Not performed | Final report: Fatty infiltration and fibrosis of right ventricle |
| **Witness observation of death** | None; found deceased after not responding to phone calls, actual DOD unknown but last interrogation 3 d prior | None; last seen alive at 17:00; found deceased at 22:00 | Multiple GTCS with vomit night before death; found deceased in bed, cold, with vomit around mouth, at 08:45 | Found unconscious at 21:48; apneic, atrial fibrillation and pulseless; never regained consciousness; extubated the next day at 23:25 | Found deceased face down in bed with grimace on face consistent with normal seizure | Multiple seizures evening prior to and morning of DOD; found deceased in (nonignited) fire pit around 22:05 with ash in mouth and airway | Last seen alive at 21:30 night before death; found deceased at 11:45, face down in bed with left arm behind back, legs bent, and blood on nose |
| **Cause of death (from death certificate or autopsy report)** | Natural death caused by seizure disorder | SUDEP with intractable seizures | No anatomic cause of death | Grand mal seizure with prolonged resuscitation | Cardiopulmonary arrest due to, or as consequence of, acute seizure | Asphyxiation due to aspiration of ash and soot due to a seizure | Cardiac arrhythmia consistent with arrhythmogenic right ventricular dysplasia |

DOD, date of death; GTCS, generalized tonic–clonic seizures; AEDs, antiepileptic drugs.
common in patients undergoing surgical treatment of their epilepsy, as well as treatment with neurostimulation.

Treatments that reduce seizure frequency appear to reduce the risk for SUDEP. Although the populations studied have key differences, the SUDEP rate of 2.0 per 1000 patient stimulation years (95% CI 0.7-5.2) among patients undergoing treatment with responsive stimulation is favorable relative to TRE patients randomized to the placebo arm of add-on drug studies (SUDEP rate of 6.1 per 1000 patient years, 95% CI 3.3-10.3),\(^1\) patients who were referred for epilepsy surgery but did not receive epilepsy surgery (SUDEP rate of 6.3 per 1000 patient years, 95% CI 1.7-16.1),\(^14\) and patients with recurrent seizures after epilepsy surgery (SUDEP rate 6.3 per 1000 patient years, 95% CI 3.0-11.6).\(^15\) The upper limit of the 95% CI for the rate of SUDEP in patients treated with the RNS System is lower than the SUDEP rate reported in another study of epilepsy surgery candidates.\(^16\) The choice to use the Annegers et al SUDEP classification system was made by the SUDEP adjudication committee, and this was the same scheme used in most studies to which we draw comparisons.

Accumulating patient experience will further refine the SUDEP rate for patients treated with the RNS System. In addition, because the RNS System gathers additional data on seizures and epileptiform activity leading to death, future explorations can examine whether certain seizure patterns are particularly associated with SUDEP.

**ACKNOWLEDGMENTS**

We thank W. Allen Hauser, Theodore Walczak, and Terri Haddix for serving on the NeuroPace SUDEP Adjudication Panel.

**DISCLOSURE OF CONFLICT OF INTEREST**

Author Orrin Devinsky, has received funding from the National Institute of Neurological Disorders and Stroke.
(NINDS) for SUDEP Research and serves as the Principal Investigator of the North American SUDEP Registry and Sudden Unexpected Death in Childhood Registry and Research Collaborative. He has received research grants from GW Pharmaceuticals, Zogenix, Novartis, and PTC Therapeutics. Author Daniel Friedman, receives support to New York University from the Epilepsy Study Consortium and consulting fees from LivaNova and UCB, Inc. He has served on advisory boards for GW Pharmaceuticals and Supernus. He receives research support from the National Institutes of Health (NIH), the Epilepsy Foundation, the Centers for Disease Control and Prevention (CDC), and UCB, Inc. He has received honoraria for education materials for NeuroPace, Inc. He serves on the executive board of the North American SUDEP Registry. Author Robert B Duckrow, has received research grants awarded to Yale University from NeuroPace. Author Nathan B Fountain, has received research grants awarded to the University of Virginia, NeuroPace, Medtronic, NIH, the Epilepsy Foundation, UCB, Lundbeck, Takeda, Neurelis, and SK Life Sciences. Author Ryder P. Gwinn, has received consulting fees from NeuroPace, Boston Scientific, and Medtronic. Author Anthony M Murro, has received research grants from NeuroPace and UCB. Author Paul C. Van Ness, has received research support from NeuroPace during the pivotal trial. The remaining authors have no conflicts of interest to disclose that are relevant to this research activity. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10:961–8.
2. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016;15:1075–88.
3. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013;12:966–77.
4. Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy; a realistic goal? Epilepsia. 2013;54(Suppl 2):23–8.
5. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. Neurology. 2016;86:779–86.
6. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015;84:810–7.
7. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014;55:432–41.
8. Annegers JF. United States perspective on definitions and classifications. Epilepsia. 1997;38:S9–12.
9. Lhatoo SD, Nei M, Rahnavan M, et al. Nonseizure SUDEP: sudden unexpected death in epilepsy without preceding epileptic seizures. Epilepsia. 2016;57:1161–8.
10. Death rates by 10-year age groups: United States and each state, 2007: Worktable 23R. https://www.cdc.gov/nchs/data/dvs/mortfinal2007_worktable 23r.pdf. Accessed October 9, 2017.
11. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Ann Neurol. 2016;79:522–34.
12. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia. 2011;52:1150–9.
13. Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy Res. 2005;65:101.
14. Nilsson L, Ahlborn A, Farahmand BY, Tomson T. Mortality in a population-based cohort of epilepsy surgery patients. Epilepsia. 2003;44:575–81.
15. Sperling MR, Harris A, Nei M, Liporace JD, O’Connor MJ. Mortality after epilepsy surgery. Epilepsia. 2005;46(Suppl 11):49–53.
16. Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. J Clin Neurophysiol. 1991;8:216–22.

How to cite this article: Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia. 2018;59:555–561. https://doi.org/10.1111/epi.13998