Title
Real-world experience with direct brain-responsive neurostimulation for focal onset seizures.

Permalink
https://escholarship.org/uc/item/7kp0g0f6

Journal
Epilepsia, 61(8)

ISSN
0013-9580

Authors
Razavi, Babak
Rao, Vikram R
Lin, Christine
et al.

Publication Date
2020-08-01

DOI
10.1111/epi.16593

Peer reviewed
**Real-world experience with direct brain-responsive neurostimulation for focal onset seizures**

Babak Razavi | Vikram R. Rao | Christine Lin | Krzysztof A. Bujarski | Sanjay E. Patra | David E. Burdette | Eric B. Geller | Mesha-Gay M. Brown | Emily A. Johnson | Cornelia Drees | Edward F. Chang | Janet E. Greenwood | Christianne N. Heck | Barbara C. Jobst | Ryder P. Gwinn | Nicole M. Warner | Casey H. Halpern

1 Stanford University School of Medicine, Stanford, CA, USA
2 University of California, San Francisco, CA, USA
3 Dartmouth Hitchcock Medical Center, Lebanon, NH, USA
4 Spectrum Health Center, Michigan State University School of Human Medicine, East Lansing, MI, USA
5 St. Barnabas Medical Center, Livingston, NJ, USA
6 University of Colorado, Denver, CO, USA
7 University of Colorado, Denver, CO, USA
8 Washington University School of Medicine, St. Louis, MO, USA
9 Keck School of Medicine at University of Southern California, Los Angeles, CA, USA
10 Swedish Neuroscience Institute, Seattle, WA, USA

**Correspondence**
Babak Razavi, Stanford University School of Medicine, 213 Quarry Road, MC 5978, Palo Alto, Stanford, CA 94304.
Email: brazavi@stanford.edu
Casey H. Halpern, Stanford University Medical Center, 300 Pasteur Drive, Edwards Building / R-227, Stanford, CA 94305
Email: chalpern@stanford.edu

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. Epilepsia published by Wiley Periodicals LLC on behalf of International League Against Epilepsy

**Abstract**

**Objective:** The RNS System is a direct brain-responsive neurostimulation system that is US Food and Drug Administration–approved for adults with medically intractable focal onset seizures based on safety and effectiveness data from controlled clinical trials. The purpose of this study was to retrospectively evaluate the real-world safety and effectiveness of the RNS System.

**Methods:** Eight comprehensive epilepsy centers conducted a chart review of patients treated with the RNS System for at least 1 year, in accordance with the indication for use. Data included device-related serious adverse events and the median percent change in disabling seizure frequency from baseline at years 1, 2, and 3 of treatment and at the most recent follow-up.

**Results:** One hundred fifty patients met the criteria for analysis. The median reduction in seizures was 67% (interquartile range [IQR] = 33%-93%, n = 149) at 1 year, 75% (IQR = 50%-94%, n = 93) at 2 years, 82% (IQR = 50%-96%, n = 38) at ≥3 years, and 74% (IQR = 50%-96%, n = 150) at last follow-up (mean = 2.3 years). Thirty-five percent of patients had a ≥90% seizure frequency reduction, and 18% of patients reported being clinically seizure-free at last follow-up. Seizure frequency reductions were similar regardless of patient age, age at epilepsy onset, duration of epilepsy, seizure onset in mesial temporal or neocortical foci, magnetic resonance imaging findings, prior intracranial monitoring, prior epilepsy surgery, or prior vagus nerve stimulation treatment. The infection rate per procedure was 2.9% (6/150 patients); five of the six patients had an implant site infection, and one had osteomyelitis. Lead revisions were required in 2.7% (4/150), and 2.0% (3/150) of patients had a subdural hemorrhage, none of which had long-lasting neurological consequences.
1 | INTRODUCTION

Neuromodulation is an important treatment option for patients with medically intractable focal onset seizures who are not optimal candidates for surgical resection or ablation due to an unfavorable risk-benefit profile or patient preference. The RNS System (NeuroPace) is the only direct brain-responsive neurostimulator for the treatment of adults with medically intractable disabling focal onset seizures with one or two seizure foci. Safety and effectiveness were demonstrated in a randomized controlled clinical trial and in a prospective open-label clinical trial over 9 years of treatment. Median percent seizure frequency reductions were 44% at 1 year, 53% at 2 years, and 75% at 9 years of treatment. Outcomes with any epilepsy therapy outside of clinical trials may differ from the preapproval experience. Experience in the RNS System clinical trials has greatly informed real-world use. The purpose of this multicenter, retrospective study was to describe the safety and efficacy of direct brain-responsive neurostimulation for adults with medically intractable focal onset seizures in the real-world setting.

2 | MATERIALS AND METHODS

Eight comprehensive epilepsy centers performed a retrospective chart review of their patients treated with the RNS System between 2013 and 2018. All study protocols were approved by the institutional review boards (IRBs) of participating centers; all IRBs waived the requirement for obtaining informed consent. All data collected before August 15, 2018 were included. Patients included in the analysis were all treated according to the US Food and Drug Administration (FDA)-approved indication.

The RNS System includes a cranially implanted neurostimulator that is connected to one or two depth or cortical strip leads, each containing four electrode contacts. The leads are placed at the seizure focus or foci. The neurostimulator continuously monitors intracranial electroencephalogram (ICEEG) and delivers stimulation in response to detections of patient-specific abnormal patterns. Continuous counts of detections, with time and location, and brief ICEEG recordings are stored for physician review. Stimulation can be delivered to eloquent areas of the brain without acute or chronic stimulation-related side effects. Detection and stimulation settings are adjusted intermittently to optimize treatment. A suggested protocol for initial stimulation programming and subsequent adjustments based on clinical trial experience is provided to all centers by the device manufacturer.

Significance: In this real-world experience, safety was similar and clinical seizure outcomes exceeded those of the prospective clinical trials, corroborating effectiveness of this therapy and suggesting that clinical experience has informed more effective programming.

KEYWORDS

brain-responsive neurostimulation, drug-resistant, medically intractable epilepsy, RNS System

Key Points

- Retrospective chart review was made of 150 patients treated with the RNS System at eight epilepsy centers
- Safety experience with the RNS System in this real-world study was comparable to clinical trials
- Median seizure frequency reductions were 67% at 1 year, 75% at 2 years, and 82% at ≥3 years
- Effectiveness outcomes with the RNS System in this real-world study exceeded those in clinical trials
A secondary outcome measure was overall impression of response to treatment using the Clinical Global Impressions Scale (CGIS), a clinician-determined summary measure of the patient’s ability to function\textsuperscript{10} that has been used in other epilepsy therapy trials.\textsuperscript{11} Antiepileptic drugs (AEDs) were also documented at each time point.

Statistical differences in outcome between the following groups were calculated using the Kruskal-Wallis test: patients with mesial temporal or neocortical seizure foci; and patients with or without magnetic resonance imaging (MRI) abnormalities, prior intracranial monitoring, prior epilepsy surgery, or prior vagus nerve stimulation (VNS) treatment. Relationships between clinical outcomes and patient age, age at epilepsy onset, or duration of epilepsy were evaluated using linear regression. The relationship between clinical outcomes and CGIS scores was also assessed. Finally, the median percent reduction in clinical seizure frequency was assessed for those who added, discontinued, or both added and discontinued AEDs. These were compared to the median percent reduction for patients who had no changes in AEDs using a Mann-Whitney \( U \) test. For all analyses, \( \alpha \) was set to .05.

## RESULTS

One hundred fifty patients were treated with the RNS System and followed for a minimum of 1 year, with mean follow-up of 2.3 years. Patient demographics are provided in Table 1. The mean age at time of implant was 39 years, and the mean duration of epilepsy was 20 years. There was a wide range in baseline seizure frequency, with a median of 7.7 disabling seizures per month (mean = 52, range = 0.1-3000 per month, SD ± 257). Patients had a variety of epilepsy etiologies, with the most common being “unknown.” MRI of the brain was abnormal for 60% of patients; the type of MRI abnormality was not captured in this study.

Sixty-seven percent of patients had two leads implanted. However, additional leads could be implanted that were not connected at the time of the initial procedure; the mean number of leads per patient was 2.6 (range = 2-5). There were seven instances (4.7%) in which there was a procedure to connect a previously unconnected lead. Of the total of 371 leads implanted, 54% were cortical strip leads and 46% were depth leads. Common lead locations and types of leads with respect to the region of seizure onset are provided in Table 2.

Sixty-five percent (\( n = 98 \)) of patients had the neurostimulator and leads implanted without ICM immediately prior. However, 49 patients (33%) had ICM electrodes explanted at the same time as the neurostimulator and leads were placed. Of these 49 patients, three patients (6%) had ICM depth electrodes only, 20 had ICM grids/strips (41%), and 26 patients (53%) had a combination of grids, strips, and depth electrodes for ICM. The mean time for ICM prior to placement of the neurostimulator and leads was 11 days (range = 3-26 days). Ten patients (7%) had resections concurrent with the neurostimulator and lead placement; seven of these 10 also had ICM electrode removal at the same time.

Once brain-responsive neurostimulation was enabled, clinic visits occurred about every 3-4 months. Stimulation was enabled postimplantation (mean = 41 days, median = 27 days, range = 2-245 days), typically after the first seizure was recorded (Figure S1). Neurostimulator settings were programmed by the physician and generally followed a manufacturer-recommended therapy protocol, with initial stimulation settings of 200 Hz, 160-microsecond pulse width, 100-millisecond burst duration, and current sufficient to achieve a charge density of 0.5 \( \mu \text{C/cm}^2 \). The total duration of stimulation was a median of 4.5 min/d (interquartile range [IQR] = 1.4-9.3 min/d). Depending on the clinical response, charge density was incrementally increased by 0.5 \( \mu \text{C/cm}^2 \) at each.

### Table 1: Patient demographics

| Total N | 150 |
|---|---|
| Gender, female, n (%) | 77 (51%) |
| Mean age, y (range) | 39 (18-69) |
| Mean duration of epilepsy, y (range) | 20 (2-60) |
| Median baseline disabling seizures per mo, n (mean; range; SD) | 7.7 (52; 0.1-3000; ±257) |
| Etiology, n (%)\textsuperscript{a} | |
| Unknown | 86 (52.1%) |
| Structural | 31 (18.8%) |
| Infection | 13 (7.9%) |
| TBI | 8 (4.8%) |
| Genetic | 6 (3.6%) |
| Head trauma | 4 (2.4%) |
| Hypoxic injury | 4 (2.4%) |
| Stroke | 5 (3.0%) |
| Pregnancy-related | 2 (1.2%) |
| Febrile convulsions | 2 (1.2%) |
| Metabolic | 2 (1.2%) |
| Immune | 2 (1.2%) |
| MRI of the brain, n (%) | |
| Abnormal | 90 (60%) |
| Normal | 60 (40%) |
| Prior intracranial monitoring, n (%) | 123 (82%) |
| Prior VNS, n (%) | 48 (32%) |
| Prior epilepsy surgery, n (%) | 49 (33%) |

\( \text{Abbreviations: MRI, magnetic resonance imaging; SD, standard deviation; TBI, traumatic brain injury; VNS, vagus nerve stimulation.} \)

\( \text{\textsuperscript{a}Some patients had more than one etiology.} \)
visit. Changes in charge density and current amplitude over time are shown in Figure 1 and are compared to similar data for patients in the treatment group of the randomized controlled Pivotal study.¹

### Efficacy outcomes

The median seizure frequency reduction was 67% (IQR = 33%-93%, n = 149) at 1-year follow-up, 75% (IQR = 50%-94%, n = 93) at 2-year follow-up, and 82% at 3 or more years of follow-up (IQR = 50%-96%, n = 38; Figure 2). At the most recent follow-up (mean = 2.3 years), the median percent seizure frequency reduction was 74% (IQR = 50%-96%, n = 150); 35% of patients had ≥90% seizure reduction, and 18% of patients reported being clinically seizure-free at the most recent follow-up. Responder rates (≥50% reduction in seizure frequency) were 66% at 1 year, 77% at 2 years, and 84% at 3 or more years. Seizure frequency reductions at 1 year were similar regardless of patient age, age at epilepsy onset, or duration of epilepsy (P > .05), location of seizure foci (mesial temporal or neocortical; P = .13), brain MRI abnormalities (P = .60), prior intracranial monitoring (P = .88), prior epilepsy surgery (P = .20), or prior VNS treatment (P = .62). Results were similar when patients who had a resection concurrent with placement of the RNS System neurostimulator and leads were excluded; median percent seizure reductions were 63% at 1 year (mean = 45%, IQR = 26%-93%), 74% at 2 years (mean = 63%, IQR = 50%-94%), and 81% at 3 or more years of follow-up (mean = 74%, IQR = 64%-98%). Reductions in seizure frequency at 1 year of follow-up were not significantly related to postimplantation days to initiate therapy (r = −.14, P = .19; Figure S1).

There was no statistically significant difference in any of the outcome results between the eight centers (P > .05). In a post hoc comparison of 2-year responder rates from this study and the open-label period of the Pivotal trial, seizure outcomes in the real-world cohort were significantly better (chi-squared proportion test, P < .05).

### Safety outcomes

Seventeen of the 150 patients (11.3%) had a total of 22 device-related serious adverse events (SAEs), as summarized in Table 3.

Six patients (4%) had infections. Of these, five patients (3.3%) had implant site soft-tissue infections; two of these five patients had the neurostimulator and leads removed, and the other three were treated with debridement, washout, and antibiotics. One patient (0.7%) had osteomyelitis that was diagnosed 18 months after the neurostimulator and lead implantation. The neurostimulator and leads were removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. Three of the six patients with infections had a neurostimulator and lead implanted as the sole procedure, and the other three patients had the neurostimulator and leads removed, and the patient was treated with intravenous antibiotics. A subsequent cranioplasty was performed, and the infection resolved. There was no statistically significant difference in the rate of infection
between the group that had the neurostimulator and leads implanted as the sole procedure (3.0%) and those who had ICM electrodes removed in the same procedure as the neurostimulator and leads were placed (6.1%, \( P = .38 \)).

Three patients had subdural hematomas. One of the three was being treated with anticoagulants because of a pulmonary embolism following placement of the RNS System neurostimulator and leads. A subsequent fall led to a subdural hematoma that required evacuation and also caused damage to a lead, which required lead revision. A second patient had a postimplant fall resulting in a subdural hematoma that was considered minor; however, the patient had an acute worsening of seizures. The third patient had a postoperative subdural hematoma and then had a procedure to remove a cortical strip lead, after which there was intraparenchymal bleeding. There were no long-lasting neurological consequences for any of these patients.

Other SAEs included one patient with a third nerve palsy noted 2 days after the RNS System neurostimulator and leads were implanted; this resolved when the subtemporal strip was retracted. Scalp erosion occurred in one patient who also had an infection at the implant site, and in a second patient near a depth lead incision. Two patients were seen in emergency departments because of changes in seizures, one with an acute worsening of seizures and a new seizure type, and the other for an increase in seizure frequency that resolved. One patient had an acute hemiparesis that immediately recovered when a cortical strip lead was removed. Because of pain, one patient had a procedure to reseat a bone screw used to secure the cranially mounted tray into which the neurostimulator is

**TABLE 3** Device-related SAEs

| SAE                      | Patients, n (%) |
|--------------------------|-----------------|
| Infection                | 6 (4.0%)        |
| Implant site soft tissue | 5 (3.3%)        |
| Osteomyelitis            | 1 (0.7%)        |
| Lead revision            | 4 (2.7%)        |
| Subdural hematoma        | 3 (2.0%)        |
| Scalp erosion            | 2 (1.3%)        |
| Worsening of seizures    | 2 (1.3%)        |
| Pulmonary embolism       | 1 (0.7%)        |
| Third nerve palsy        | 1 (0.7%)        |
| Hemiparesis              | 1 (0.7%)        |
| Incision site pain       | 1 (0.7%)        |
| Pseudomeningocele        | 1 (0.7%)        |

Abbreviation: SAE, serious adverse event.

*Some patients had more than one SAE.
seated; a cortical strip lead was added at the time of the re-
vision, because the patient only had one lead placed at the 
original implant. Another patient had a ventriculoperitoneal 
shunt placed because of a persistent pseudomeningocele that 
resolved; the shunt was subsequently weaned and removed.

There were two patient deaths, neither of which was con-
sidered to be related to treatment with the RNS System. One 
patient with a history of depression and suicidality commit-
ted suicide. Another patient died as a result of renal cancer.

3.3 | Secondary outcomes

The CGIS was completed for 140 of 150 (93%) patients. 
At the most recent follow-up, 75% of patients were rated 
by their physician as “very much improved” or “much im-
proved,” 14 patients (10%) as having “no change,” and three 
patients (2%) as minimally or much worse (Figure 3). There 
was a significant positive correlation between CGIS and per-
cent change in seizure frequency at last follow-up ($r = .39$, 
n = 140, $P = .00001$).

One of the two patients considered to be “minimally 
worse” had no improvement in seizure frequency and a de-
crease in cognitive function; it was not known whether this 
was related to continued seizures or to the RNS System. The 
other had an increase in seizures and an implant site infec-
tion that required device explantation. The patient described 
as “much worse” had no seizure reduction with the RNS 
System, developed osteomyelitis 18 months postoperatively, 
and eventually required explantation of the neurostimulator 
and leads.

AEDs were not changed in 45% (67/150) of patients 
during the study. Sixteen percent (24/150) had at least one 
AED discontinued, and 12% (18/150) had at least one added. 
An additional 27% (41/150) had at least one AED added and 
discontinued during the study. The changes in seizure fre-
quency at last follow-up were not different between these 
groups ($P > .05$).

4 | DISCUSSION

This multicenter, real-world, retrospective review provides 
the first report on effectiveness of direct brain-responsive 
neurostimulation outside of the clinical trials that supported 
FDA approval of the RNS System. Seizure frequency reduc-
tions of 67% at 1 year and 75% at 2 years of treatment in 
the real-world cohort are similar to the seizure reductions 
achieved at 6 and 9 years of treatment in the clinical trials.2,3 
Other neuromodulation therapies for epilepsy also show pro-
gressive reductions in seizure frequency over time in both 
clinical trial and real-world environments.12–14

Our findings support the use of direct brain-responsive 
neurostimulation therapy for medically refractory patients with 
focal onset seizures. Despite the introduction of many AEDs, 
the likelihood of achieving seizure freedom with additional 
trials of AEDs after failing the first two AEDs is <5%,15 and 
the patient remains at risk for AED-related adverse events.16 
Furthermore, if a seizure onset zone can be localized, surgical 
resection or ablation of the tissue can result in seizure remis-
sion for 52%-65% of patients, depending on the location.17–20 
However, if two areas of seizure onset are identified, the onset 
zone overlaps with eloquent cortex, the tissue cannot be safely 
or completely resected or ablated, or the patient declines resec-
tion or ablation, direct brain-responsive neurostimulation may 
be considered.21 Moreover, patients may prefer to attempt a 
reversible neuromodulatory treatment approach prior to con-
sidering irreversible resection or ablation.

Infection rates were 2.9% per procedure, similar to those 
observed in the RNS System clinical trials (4.1% per pro-
cedure), and are consistent with infection rates reported with 
other implanted devices for epilepsy13 and movement dis-
orders.22–25 The rate of infection in patients who had ICM 
electrodes explanted at the same time as the neurostimulator 
and leads were placed (6.1%) compares favorably to those 
in patients who have undergone only intracranial monitoring 
(5.7%)26 or resection for epilepsy (2.1%-8.5%).27 Because the 
risks and types of infection are not significantly higher when 
the RNS System implant procedure occurs in association with 
intracranial monitoring or concurrent with a resection, poten-
tial benefits of these combined approaches can be weighed 
against the potential additive infection risks associated with 
multiple surgeries.

The incidence and types of intracranial hemorrhage 
in this real-world cohort were also similar to the clinical 
trials of the RNS System (2.1% in the 2-year randomized 
controlled trial7 and 2.7% over long-term follow-up8) and 
to published experience with deep brain stimulation for
epilepsy and movement disorders. Procedure-related hemorrhages did not result in long-lasting medical or neurological consequences.

There are several possible explanations for the rapid and robust real-world response to treatment with direct brain-responsive neurostimulation relative to the initial clinical trials. Greater efficacy in real-world applications compared to clinical trial experience is also described with AEDs. This has been postulated to be because patients in the real world may have less severe epilepsy than patients who choose to participate in clinical trials. This is not the likely explanation in this case, because demographics and disease-related characteristics of the real-world patients were very similar to the patients in the RNS System clinical trials, including age, duration of epilepsy, baseline seizure frequency, region of seizure onset, types and locations of leads, and the percent of patients previously treated with VNS or resective surgery. In the randomized controlled Pivotal trial, 59% of patients had prior intracranial monitoring, compared to 82% in this real-world cohort. Although it is possible that this contributed to improved outcome, there was no difference in outcomes in the Pivotal and Long-Term Treatment trials between patients who had or had not undergone intracranial monitoring.

Another potential explanation is that accumulated experience in the clinical trials has informed more efficient and effective detection and stimulation programming strategies, which have evolved with clinical experience. In the initial clinical trials, study protocols required at least 10 visits over the first 24 months after implantation, and programming was often changed at each of these visits. In current clinical practice, patients are usually seen 6-8 times over the first 24 months and stimulation is not generally adjusted at every visit. Contemporary practice recognizes that a change in clinical seizure frequency may not be evident for 2-4 months after a reprogramming. Thus, more frequent programming may obscure a favorable seizure response. Charge density, which is a function of the current amplitude and the stimulation pathway configuration, was also different, with more gradual increase in current and lower overall charge density in the real-world patients than in the early clinical trials. Another difference between the clinical trials and present-day practice is that detection is programmed so that stimulation is delivered in response to activity typically preceding seizures, such as a run of epileptiform spikes or changes in amplitude or rhythmicity, rather than clearly developed electrographic seizures. Stimulating into well-developed electrographic seizures may not always disrupt electrographic seizure activity, perhaps because the seizure has already propagated beyond the region that can be impacted by spatially limited stimulation. It is possible that delivering acute disruptive stimulation into abnormal (interictal) electrographic activity (not only seizures) is effective because of providing longer-term neuromodulation. This hypothesis is supported by the observation that the total duration of stimulation received was a median of 4.5 min/d (IQR = 1.4-9.3 min/d) in the real-world patients, which is significantly greater than in the Pivotal trial population (median = 3.0 minutes of stimulation per day, IQR = 1.5-5.1 min/d) at 2 years postoperatively (P = .024), although substantially less than with open-loop scheduled stimulation approaches.

This study has limitations, including the retrospective nature of data collection and that patient-reported seizure counts—although still a gold standard outcome measure for epilepsy clinical trials—are unreliable. Seizures may be undercounted in the real world compared to clinical trials in which daily entries into a seizure diary are required, but within-patient comparison to preimplant seizure frequency may mitigate this concern. Another limitation is that seizure severity was not captured due to inconsistent assessment across centers. However, the CGIS is an accepted instrument for measuring overall response to an intervention and represents the physician's perception of changes in the total burden of seizures. The significant positive correlation between CGIS and changes in patient-reported seizure frequency lends credence to this metric.

The expectation of benefit may be higher in patients who know they will be receiving active treatment compared to patients in randomized controlled trials in which some fraction will receive placebo. In the RNS System randomized controlled Pivotal trial, 50% were randomized to sham stimulation and did not receive active stimulation until 6 months after implant. However, at 6 months, all patients entered an open-label period and knew that they were receiving neurostimulation. Therefore, patients in the open-label periods of the prospective clinical trials also knew that they were receiving stimulation, so the expectation of benefit can be reasonably assumed to be similar to these patients treated outside of clinical trials. Thus, the improved efficacy in the real world is likely independent of differences in patient expectation.

Real-world patients with long-standing epilepsy and disabling focal onset seizures resistant to multiple different treatments experienced substantial and sustained reduction in seizure frequency with direct brain-responsive neurostimulation. The safety experience was similar to the clinical trials of the RNS System and of other brain stimulation devices. In current practice with brain-responsive neurostimulation, clinical seizure outcomes exceeding those of the prospective clinical trials are achieved years earlier, corroborating effectiveness of this therapy and suggesting improvement in treatment efficiency.

ACKNOWLEDGMENTS
We would like to acknowledge Martha Morrell, MD, Tara Skarpaas, PhD, and Emily Mirro from NeuroPace for
providing the Pivotal trial data and for facilitating the data collection, analysis, and manuscript review.

CONFLICT OF INTEREST
B.R. has received research support from NeuroPace. V.R.R. has received support from and/or has served as a paid consultant for NeuroPace. S.E.P. has received support from and/or has served as a paid consultant for NeuroPace and Boston Scientific Corporation. D.E.B. has received support from and/or has served as a paid consultant for Greenwood Pharmaceuticals, Eisai Co, Sunovion Pharmaceuticals, NeuroPace, SK Biopharmaceuticals, UCB, and Zogenix. E.B.G. has received support from and/or has served as a paid consultant for NeuroPace, LivaNova, and Xenon Pharmaceuticals. J.E.G. is a prior employee of NeuroPace and has equity ownership/stock options. C.N.H. has received support from and/or has served as a paid consultant for NeuroPace in the form of research sponsorship of the long-term post-market outcomes. B.C.J. has received support from and/or has served as a paid consultant for NeuroPace for the Pivotal trial. E.B.G. has received support from and/or has served as a paid consultant for NeuroPace's Scientific Advisory Council. C.H.H. has received support from and/or has served as a paid consultant for Boston Scientific Corporation. The remaining authors have no conflicts of interest. 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.

ORCID
Babak Razavi https://orcid.org/0000-0002-8623-8161
Vikram R. Rao https://orcid.org/0000-0002-6389-2638
Krzysztof A. Bujarski https://orcid.org/0000-0002-1329-5085
Mesha-Gay M. Brown https://orcid.org/0000-0003-2470-3723
Cornelia Drees https://orcid.org/0000-0002-9977-983X
Casey H. Halpern https://orcid.org/0000-0003-3907-216X

REFERENCES
1. Morrell MJ, RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77:1295–304.
2. 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.
3. Nair DR, RNS System Investigators, Morrell MJ, et al. Nine-Year Prospective Safety and Effectiveness Outcomes From the Long-Term Treatment Trial of the RNS® System. Poster session presented at: 72nd Annual Meeting of the American Epilepsy Society; New Orleans, LA.
4. Lhatoo SD, Wong IC, Polizzi G, Sander JW. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. Epilepsia. 2000;41:1592–6.
5. Morrell MJ, Leppik I, French J, Ferrendelli J, Han J, Magnus L. The KEEPER trial: levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study. Epilepsy Res. 2003;54:153–61.
6. Sander JW. New antiepileptic drugs in practice—how do they perform in the real world? Acta Neurol Scand Suppl. 2005;181:26–9.
7. Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia. 2017;58:994–1004.
8. Jobst BC, Kapur R, Barkley GL, et al. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia. 2017;58:1005–14.
9. Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuro-psychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia. 2015;56:1836–44.
10. Busner J, Targum SD. The Clinical Global Impressions Scale. Psychiatry (Edgmont). 2007;4:28–37.
11. Chaves J, Breia P, Pimentel J, et al. Eslicarbazepine acetate as adjunctive therapy in clinical practice: ESLADOBA study. Acta Neurol Scand. 2017;136:407–13.
12. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg. 2011;115:1248–55.
13. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84:1017–25.
14. Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotact Funct Neurosurg. 2012;90:379–85.
15. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
16. Mahajan UV, Parker JJ, Williams NR, et al. Adjunctive repetitive transcranial magnetic stimulation delivers superior quality of life for focal epilepsy compared to anti-epileptic drugs: a meta-analytic utility prediction study. Brain Stimul. 2020;13:430–2.
17. Engel J, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology. 2003;60:538–47.
18. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011;378:1388–95.
19. Wiebe S, Blume WT, Girvin JP, Eliaziw M. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345:311–8.
20. Wu C, Jermakowicz WJ, Chakravorti S, et al. Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: a multicenter study of 234 patients. Epilepsia. 2019;60:1171–83.
21. Ma BB, Rao VR. Responsive neurostimulation: candidates and considerations. Epilepsy Behav. 2018;88:388–95.
22. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301:63–73.
23. Ghosh PS, Machado AG, Deogaonkar M, Ghosh D. Deep brain stimulation in children with dystonia: experience from a tertiary care center. Pediatr Neurosurg. 2012;48:146–51.
24. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. J Neurosurg Pediatr. 2011;8:566–74.
25. Deep-Brain Stimulation for Parkinson’s Disease Study Group, Obeso JA, Olanow CW, et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson’s disease. N Engl J Med. 2001;345:956–63.
26. Schmidt RF, Wu C, Lang MJ, et al. Complications of subdural and depth electrodes in 269 patients undergoing 317 procedures for invasive monitoring in epilepsy. Epilepsia. 2016;57:1697–708.
27. Georgiadis I, Kapsalaki EZ, Fountas KN. Temporal lobe resective surgery for medically intractable epilepsy: a review of complications and side effects. Epilepsy Res Treat. 2013;2013:752195.
28. Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol. 2019;76:800–8.
29. Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology. 1996;47:260–4.
30. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav. 2012;24:304–10.
31. Hoppe C, Poespel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol. 2007;64:1595–9.
32. Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. Epilepsy Behav. 2006;9:281–5.
33. Tatum WO, Winters L, Gieron M, et al. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. J Clin Neurophysiol. 2001;18:14–9.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.