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Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation

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ABSTRACT

Purpose: The primary efficacy and safety measures from a trial of responsive neurostimulation for focal epilepsy were previously published. In this report, the findings from the same study are presented for quality of life, which was a supportive analysis, and for mood, which was assessed as a secondary safety endpoint.
Methods: The study was a multicenter randomized controlled double-blinded trial of responsive neurostimulation in 191 patients with medically resistant focal epilepsy. During a 4-month postimplant blinded period, patients were randomized to receive responsive stimulation or sham stimulation, after which all patients received responsive neurostimulation in open label to complete 2 years. Quality of life (QOL) and mood surveys were administered during the baseline period, at the end of the blinded period, and at year 1 and year 2 of the open label period.
Results: The treatment and sham groups did not differ at baseline. Compared with baseline, QOL improved in both groups at the end of the blinded period and also at 1 year and 2 years, when all patients were treated. At 2 years, 44% of patients reported meaningful improvements in QOL, and 16% reported declines. There were no overall adverse changes in mood or in suicidality across the study. Findings were not related to changes in seizures and antiepileptic drugs, and patients with mesial temporal seizure onsets and those with neocortical seizure onsets both experienced improvements in QOL.
Conclusions: Treatment with targeted responsive neurostimulation does not adversely affect QOL or mood and may be associated with improvements in QOL in patients, including those with seizures of either mesial temporal origin or neocortical origin.

1. Introduction

Persons with epilepsy face challenges beyond the direct effects of seizures. Epilepsy therapy trials typically consider change in seizure frequency to be the primary indicator of effectiveness. However, counting seizures does not adequately reflect other important treatment effects on a patient's life experience, and increasingly, characterization of treatment effectiveness in epilepsy includes quality of life (QOL) and emotional health. In the present report, quality of life and mood were assessed in subjects participating in a randomized, double-blind, multicenter, controlled trial of a responsive neurostimulator for the treatment of medically intractable partial-onset seizures.

Targeted responsive stimulation using a cranially implanted neurostimulator (RNS® System, NeuroPace, Mountain View, CA) was recently approved by the FDA for the adjunctive treatment of medically intractable frequent partial-onset seizures in adults with one or two seizure foci [1,2]. The programmable neurostimulator continuously senses electrocorticographic activity through depth and/or cortical strip leads placed at the seizure focus or foci and delivers responsive stimulation when physician-specified electrocorticographic patterns are detected. Treatment with the RNS System reduced the frequency of medically intractable disabling partial-onset seizures in adults, and the safety of the implant procedure and responsive stimulation therapy was acceptable compared with comparable procedures. Here, the findings from that study are presented for quality of life, which was a supportive effectiveness analysis in the trial, and for mood, which was assessed as a secondary safety endpoint.

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2. Methods

2.1. Randomized, double-blind, multicenter, controlled trial

Eligible subjects were 18–70 years old; had 3 or more simple partial motor, complex partial, or secondarily generalized tonic–clonic seizures on average each month; had seizures which failed to substantially improve with at least 2 antiepileptic medications; and had seizures coming from 1 focus or 2 foci as identified using the standard procedures for localization at that investigational site. Patients with an active psychosis, an unstable major depressive disorder, or suicidal ideation in the previous year were excluded, but patients with a prior history of any of these, or with a stable depressive disorder, could be enrolled.

After a 3-month baseline, subjects were implanted with the responsive neurostimulator and leads, and detection was enabled. One month after implantation, subjects were randomized 1:1 to receive stimulation in response to detections (treatment group) or to continue detection without stimulation (sham group) for another 4 months (blinded period). Thereafter, all subjects received responsive stimulation through the end of the two-year study (open label period).

2.2. Behavioral surveys

Quality of life and mood surveys were administered during the baseline period, at the end of the blinded period, and at 1 year and 2 years during the open label period. Surveys were reviewed by a neuropsychologist blinded to randomization. Data were excluded from the analysis if the administration date of the survey was more than 6 weeks from the per protocol visit date or if the survey was missing ≥15% of the items. Differences between the treatment group and the sham group were assessed using 2-sample *t*-tests. Differences from baseline were assessed using paired *t*-tests.

Quality of life was assessed using the Quality of Life in Epilepsy Inventory — 89 (QOLIE-89) scoring manual [3]. QOLIE-89 scores were analyzed for all subjects who took the QOLIE-89 at both baseline and per protocol time points of interest. Because the QOLIE-89 generates 17 primary scale scores and an overall QOLIE-89 score as well as 4 derived subscales for Epilepsy-Targeted, Cognitive, Mental Health, and Physical Health [4] were analyzed to limit multiple comparisons. Subscale scores were not calculated if any of the primary scale scores were missing. Quality of life was characterized as meaningfully changed based upon difference scores of 5 or more points in t-score, which is equivalent to a change of 0.5 standard deviations [5].

Current symptoms of depression were assessed using the Beck Depression Inventory [6] and the Profile of Mood States [7]. The criterion for moderately severe symptoms of depression was a BDI-II score ≥ 20. Suicidality was assessed for all subjects who answered question 9 on the BDI-II, whether or not the BDI-II survey was otherwise complete. Response options were as follows: {0} I don't have any thoughts of killing myself; {1} I have thoughts of killing myself, but I would not carry them out; {2} I would like to kill myself; and {3} I would kill myself if I had the chance. Patients were categorized as endorsing suicidality if their response to question 9 on the BDI-II was greater than {0}.

2.3. Analysis of relationship of QOL to mood, seizures, and changes in antiepileptic drugs

Seizures were recorded in seizure diaries. The percent change in seizures was calculated by comparing the seizure rates in the last 3 months of the blinded period, year 1, and year 2 with the rate in the 3-month baseline. The relationship between the percent change in seizures, change in the QOLIE-89 overall score, and change in the BDI-II total scores was assessed using both univariate linear regression and multivariate linear regression.

For analysis of changes in antiepileptic drugs (AEDs), changes made in the 3 months leading up to the year 2 time point (relative to baseline) were categorized for each subject as follows: Increased AEDs if an AED was added or if dose was increased by >25% and there were no AED discontinuations or dose decreases of >25%; Decreased AEDs if an AED was discontinued or if dose was decreased by >25% and there were no new AEDs or dose increases of >25%; Both Increased and Decreased AEDs if there were new AEDs and/or dose increases as well as discontinued AEDs and/or decreases in dose; and No Change if there were no dose changes of >25% and there were no new or discontinued AEDs. The relationship between AED change category, change in the QOLIE-89 overall score, and change in the BDI-II total score was assessed using both univariate linear regression and multivariate linear regression.

3. Results

3.1. Subject demographics

Subject demographics are presented in Table 1. There were no significant demographic differences between patients randomized to the treatment group and to the sham group. Subjects had a long duration of epilepsy, and most were taking multiple daily AEDs. Approximately one third of the sample had previously been treated with the vagus nerve stimulator (VNS) and/or epilepsy surgery, and approximately 60% had previously undergone implantation of intracranial electrodes for seizure localization. Seizure onset was in the mesial temporal lobe (MTL) in 95 of the 191 subjects; 69 of the 95 had bilateral MTL seizure foci. Seizure onset was neocortical in 81 subjects, with frontal (n = 27) and lateral temporal (n = 26) being the most common. Fifteen subjects had seizures arising from both MTL and neocortical structures.

3.2. Quality of life

At baseline, QOLIE-89 overall scores (Table 2) were significantly lower than the population norms for patients with epilepsy ($p < 0.001$, one-sample *t*-test) [4]. There was no difference between treatment and sham group scores on the QOLIE-89 at baseline. Both groups had statistically significant improvements in overall scores at the end of the blinded period, with no significant difference between the groups.

Quality of life continued to improve at years 1 and 2 of the open label period and remained significantly higher than at baseline (Fig. 1, Table 2). In order to test whether these results were due to a change in group composition, a constant cohort analysis was performed using

Table 1
Demographic and baseline characteristics of implanted subjects. Demographic characteristics of all implanted patients at the time of enrollment in the pivotal trial. SD = standard deviation; AEDs = antiepileptic drugs; EEG = electroencephalogram; VNS = vagus nerve stimulator.

Characteristics	All implanted patients (N = 191)
	Mean ± SD (min–max) or % (n)
Age in years	34.9 ± 11.6 (18–66)
Female	48% (91)
Duration of epilepsy (years)	20.5 ± 11.6 (2–57)
Number of AEDs at enrollment	2.8 ± 1.2 (0–8)
Mean seizure frequency during preimplant period (seizures/month)	34.2 ± 61.9 (3–338) median = 9.7
Seizure onset location — mesial temporal lobe only (vs. others)[a]	50% (95)
Number of seizure foci — two (vs. one)[a]	55% (106)
Prior therapeutic surgery for epilepsy[a]	32% (62)
Prior EEG monitoring with intracranial electrodes	59% (113)
Prior VNS	34% (64)

[a] Characteristics used as strata in randomization algorithm.