Mood and quality of life in patients treated with brain-responsive neurostimulation: The value of earlier intervention

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Abstract

Objective: To establish whether earlier treatment using direct brain-responsive neurostimulation for medically intractable focal-onset seizures is associated with better mood and Quality of Life (QoL) compared to later treatment intervention.

Methods: Data were retrospectively analyzed from prospective clinical trials of a direct brain-responsive neurostimulator (RNS System) for treatment of adults with medically intractable focal-onset epilepsy. Participants completed the Quality of Life in Epilepsy Inventory (QOLIE-31) yearly through 9 years of follow-up and the Beck Depression Inventory-II (BDI-II) through 2 years of follow-up. Changes in each assessment after treatment with responsive neurostimulation were calculated for patients who began treatment within 10 years of seizure onset (early) and those who began treatment 20 years or more after seizure onset (late).

Results: The median duration of epilepsy was 18.3 years at enrollment. At 9 years, both the early (N = 51) and late (N = 109) treatment groups experienced similar and significant reductions in the frequency of disabling seizures (73.4% and 77.8%, respectively). The early treatment patients had significant improvements in QoL and mood. However, the late treatment patients not only failed to show these improvements but also declined in the emotional QoL subscale.

Conclusions: Patients treated with brain-responsive neurostimulation earlier in the course of their epilepsy show significant improvements in multiple domains of QoL and mood that are not observed in patients treated later in the course of their epilepsy despite similar efficacy in seizure reduction. Even with similar and substantial reductions in seizure frequency, the comorbidities of uncontrolled epilepsy may be less responsive to treatment when too many years have passed. The results of this study suggest that, as with resective and ablative surgery, treatment with brain-responsive neurostimulation should be delivered as early as possible in the course of medically resistant epilepsy to maximize the opportunity for improvements in mood and QoL.

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1. Introduction

Epilepsy is one of the most common neurological disorders, afflicting approximately 1% of the population [1–3]. Antiseizure medications (ASMs) fail to control seizures in about 40% of patients with focal-onset epilepsy [4]. Treatment options for ASM-resistant epilepsy include surgery to resect or ablate the seizure focus and neuromodulation therapies. However, patients are often not considered for non-pharmacologic treatments until they are formally evaluated in a comprehensive epilepsy center, which unfortunately is often 20 years or more after epilepsy onset [5]. Surgical resection or ablation of the seizure focus is the preferred treatment option for patients with medically refractory seizures, whose seizure focus can be localized and the planned resection would not involve an eloquent brain area [6–10]. The
likelihood of seizure freedom is higher in patients with a shorter duration of epilepsy (<10 years) at the time of surgery, regardless of region of seizure onset [11,12] or etiology [13,14]. Older patients and patients who have had epilepsy longer [11,15,16] at the time of surgery are more likely to have seizures recur, although this relationship is not always observed [17]. Additionally, patients who undergo surgery at a later age are less satisfied with their QoL than younger surgical patients, particularly in the QoL domains of role activities, memory function, leisure activities, and emotional well-being [18].

Despite the clear benefits of earlier intervention, epilepsy surgery is often delayed for 20 years or more after initial epilepsy diagnosis [19,20]. Nearly half of this delay, however, may be accounted for by the ~9 years it can take for medical intractability to be established [19]. Protracted evaluation is influenced by age of seizure onset (e.g. longer delays to epilepsy surgery with younger age of onset) but also may be necessary to evaluate ASM treatment success given the unreliability of subjective seizure reports [21,22] and the remitting and recurring nature of the disorder.

For adults with medically refractory focal epilepsy who are not appropriate candidates for traditional resective or ablative procedures, neurostimulation provides a safe and effective treatment option [23]. The NeuroPace® RNS® System provides direct brain-responsive stimulation to the seizure focus or onset region triggered by the detection of abnormal intracranial EEG activity, which is defined for each patient by the physician [24]. Clinical trials totaling nearly 1,900 patient-implant-years demonstrate that brain-responsive neurostimulation is acceptably safe, reduces seizure frequency, and is associated with improved QoL, mood, and cognition [25–28]. To test whether earlier treatment with responsive neurostimulation also results in better QoL and mood, we retrospectively analyzed QoL and mood outcomes of patients in the RNS System clinical trials who began treatment with responsive neurostimulation within 10 years vs. after 20 or more years of poorly controlled seizures.

2. Methods

All 256 patients in this retrospective analysis participated in at least 1 of the initial clinical trials of the RNS System (NeuroPace, Inc., Mountain View CA); this included 191 patients from the 2-year randomized controlled Pivotal study, 65 from the 2-year Feasibility study, and 230 patients who transitioned from one of these studies into a 7-year follow-on long-term treatment trial [28]. The protocols for each of the trials were approved by local institutional review boards, and all patients gave informed consent (registered at www.clinicaltrials.gov NCT00264810, NCT 00079781, and NCT00572195).

Quality of Life was assessed yearly using the Quality of Life in Epilepsy Inventory (QOLIE-89), with the final assessment obtained at 9 years. For this retrospective study, we derived the QOLIE-31 scores from the QOLIE-89 assessments. In addition to the QOLIE-31 summary score, cognitive, emotional, energy, medication effects, overall (two question), seizure worry, and social function subscales were calculated [29]. Mood, assessed using the Beck Depression Inventory-II (BDI-II) [30], was evaluated at study-specific time points during the Pivotal trial, with the final assessments performed at 2 years. Baseline scores obtained 3 months before treatment with the RNS System were compared to the scores at each year up to the last timepoint at which they were assessed (treatment year 9 for the QOLIE-31, and treatment year 2 for the BDI-II). Interval change scores were computed for patients who began treatment <10 years after epilepsy onset (early) and those who began treatment ≥20 years after epilepsy onset (late). The 10-year cutoff for the early group was chosen based upon prior epilepsy studies [12], and the 20-year cutoff for the late treatment group was chosen because it is the average duration of epilepsy prior to treatment in the RNS System clinical trials [28].

Change scores in QOLIE-31 and BDI-II scores were roughly normally distributed; thus, paired 2-tailed t-tests were used to test for statistically significant changes within each group, and two-sample 1-tailed t-tests were used to test for differences between groups. One-tailed tests were used for comparing the early and late groups because the alternative hypothesis was that the early group would have better outcomes given the established literature using other epilepsy treatments. Seizure frequency was obtained from patient-maintained seizure diaries, and reductions were computed as a percentage relative to each patient’s 3-month pre-implant baseline. Percent reductions in seizure frequency were not normally distributed, and thus were compared across groups using the Mann—Whitney U-test. One-tailed Chi-square proportion tests were used to compare ratios across groups. Alpha was set to 0.05 for all analyses. No control for Type I error rate was made since failure to observe potential meaningful effects in this context (i.e., exploratory analysis, novel treatment effects in unique patient sample) is considered to be a bigger risk than reporting chance findings, which assumes completely random distributions of scores [31,32].

3. Results

Across all 256 patients in the RNS System clinical trials, the average duration of epilepsy was 19.7 ± 11.4 years. Of these patients, 51 began treatment <10 years after epilepsy onset (early), and 109 began treatment ≥20 years after epilepsy onset (late). Patient demographics for both early and late groups that completed each inventory are provided in Table 1. There were 145 patients who completed the BDI-II at baseline and 2 years (27 early and 70 late) and 145 patients who completed the QOLIE-31 at both baseline and 9 years (32 early and 72 late).

Means and standard errors of baseline and follow-up scores are presented in Table 2 for the early and late treatment groups. Early vs. late groups differed in their treatment-related changes in QOLIE-31 and BDI-II scores. Improvements in QOLIE-31 summary scores and mood were significantly greater in the early treatment group than in the late treatment group (Fig. 1), as were improvements across all QoL subdomains (Table 2). Patients in the late treatment group, with the exception of the subdomain of seizure worry, did not improve in most aspects of QoL or in mood, and in fact, declined in the emotional QoL subdomain (Table 2).

Fig. 2 shows the average QOLIE-31 summary score at each timepoint for each group, the change in QoL scores relative to baseline at each timepoint, and the patient-by-patient change from baseline to year 9 for patients who completed the QOLIE-31 at both timepoints. The improvement in QOLIE-31 summary scores was significantly greater in the early group than the late group in year 4 (p < 0.05) and then again for years 6–9 (p < 0.05) (Fig. 2B). Of the 32 patients in the early treatment group who completed the QoL assessment at both timepoints, 23 (71.9%) had a meaningful improvement in QoL, as characterized by the Minimal Clinically Important Difference (MCID) of ½ standard deviation (i.e., 5T points) [33]. Only 19 of 72 (26.4%) late treatment patients showed a meaningful improvement, which is a significantly smaller fraction (1-tailed Chi-square proportion test, χ² = 19.0; p < 10⁻⁶).

Fig. 3 shows the average BDI-II score at each timepoint, the change in BDI-II relative to baseline at each timepoint, and the patient-by-patient changes from baseline to year 2 for patients who completed the mood assessment at both timepoints. Of the 27 patients in the early treatment group who completed the BDI-II at both timepoints, 15 (55.5%) had a MCID improvement in
Table 1
Average age at enrollment and duration of epilepsy for the sample population for each assessment.

| Assessment | Demographic Feature | All | Early | Late |
|------------|---------------------|-----|-------|------|
| QOLIE-31  | Sample Size         | 145 | 32    | 72   |
|           | Average age at enrollment (SD) | 34.0 (11.0) | 29.3 (11.8) | 38.0 (9.5) |
|           | Average duration (SD)     | 19.7 (10.8) | 6.2 (2.0) | 28.4 (7.8) |
|           | % MTL (N)              | 45.5 (66) | 53.1 (17) | 43.1 (31) |
|           | % Neocortical (N)       | 46.2 (67) | 40.6 (13) | 51.4 (37) |
|           | % with Anatomical Abnormality on MRI (N) | 66.2 (96) | 62.5 (20) | 68.1 (40) |
|           | % Prior Intracranial Monitoring (N) | 66.9 (97) | 59.4 (19) | 70.8 (51) |
|           | % Prior Resection (N)    | 29.7 (43) | 9.4 (3) | 31.9 (23) |
|           | % Prior VNS (N)         | 27.6 (40) | 6.3 (2) | 29.2 (21) |
| BDI-II    | Sample Size           | 145 | 27   | 70   |
|           | Average age at enrollment (SD) | 34.5 (11.3) | 29.3 (11.3) | 38.8 (10.3) |
|           | Average duration (SD)   | 20.2 (11.0) | 6.1 (1.9) | 29.3 (8.2) |
|           | % MTL (N)              | 48.3 (70) | 48.1 (13) | 45.7 (32) |
|           | % Neocortical (N)       | 44.1 (64) | 44.4 (12) | 47.1 (33) |
|           | % with Anatomical Abnormality on MRI (N) | 65.5 (95) | 62.9 (17) | 68.6 (48) |
|           | % Prior Intracranial Monitoring (N) | 60.7 (88) | 55.6 (15) | 67.1 (47) |
|           | % Prior Resection (N)    | 30.3 (44) | 7.4 (2) | 32.9 (23) |
|           | % Prior VNS (N)         | 33.8 (49) | 11.3 (3) | 35.7 (22) |

Table 2
Statistics of each score, comparing the early and late groups at the last time point. The mean change, standard error of the mean (SE), and number of patients (N) are shown for each group and each score, in the same order as the data in the bar graphs displayed in Figs. 1 and 2. The last 3 columns show the effect size (Cohen’s d, early – late), t score, and P-value resulting from a one-tailed t test comparing the early and late groups.

| Score                     | Mean change ± SEM (N), early group | Mean change ± SEM (N), late group | Effect size (Cohen’s d) | t score | P-value |
|---------------------------|-----------------------------------|----------------------------------|------------------------|---------|---------|
| QOLIE-31 summary score    | 8.4 ± 1.6 (32)                    | −0.4 ± 1.0 (72)                   | 0.98                   | 4.59    | <0.0001 |
| Cognitive                 | 0.5 ± 1.3 (32)                    | −0.2 ± 1.2 (72)                   | 0.76                   | 3.38    | 0.0005  |
| Emotional                 | 0.8 ± 1.8 (32)                    | −0.6 ± 1.2 (72)                   | 0.57                   | 2.76    | 0.0035  |
| Energy                    | 4.2 ± 1.6 (32)                    | −1.9 ± 1.2 (72)                   | 0.64                   | 2.94    | 0.002   |
| Medication                | 5.1 ± 2.0 (32)                    | −0.7 ± 1.2 (72)                   | 0.54                   | 2.58    | 0.006   |
| Overall                   | 4.1 ± 2.1 (32)                    | −0.9 ± 1.4 (72)                   | 0.42                   | 1.98    | 0.025   |
| Seizure worry             | 1.1 ± 2.0 (32)                    | 4.2 ± 1.0 (72)                    | 0.67                   | 3.36    | 0.0005  |
| Social Function           | 8.3 ± 1.9 (32)                    | 1.1 ± 1.0 (72)                    | 0.74                   | 3.63    | 0.0002  |
| BDI-II                    | −5.3 ± 2.2 (27)                   | −0.3 ± 1.0 (70)                   | −0.56                  | −2.46   | 0.0079  |

Fig. 1. QoL and mood improve more in patients with epilepsy treated earlier. (A) QOLIE-31 (QoL) summary score. Left, change in QoL score between baseline and year 9 of treatment for each patient who completed the QoL assessment at both years, plotted as a function of that patient’s duration of epilepsy. Dotted line is the linear fit to the data. Right, the mean and standard error of the mean (SEM) of the change in QoL scores for patients who had epilepsy for <10 years vs. ≥20 years before beginning treatment. (B) Same as (A), for the change in the BDI-II (BDI) score from baseline to year 2 of treatment. Note that a higher QoL score indicates better QoL, but a lower BDI-II score indicates better mood. Statistical significance key: n.s.: not significant (P ≥ 0.05); *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

mood, as defined by the National Institute for Health and Care Excellence as a decrease in BDI-II score of at least 3 points [34]. Of the 70 patients in the late treatment group, only 27 (38.6%) showed a meaningful MCID improvement. The difference in these ratios did not reach statistical significance (1-tailed Chi-square proportion test, χ² = 2.29; P = 0.065).

We also tested whether age at onset of epilepsy was related to QoL and mood outcomes, separating patients by <22 years of age at onset (younger) vs. ≥22 years (older), chosen based on FDA’s definition of pediatric vs. adult. Similar trends occurred when grouping patients by pediatric or adult onset of epilepsy (Supplementary Fig. 1), but effect sizes were smaller for age than for epilepsy duration and did not reach statistical significance. However, the lack of significant differences may partially be explained by the lower statistical power due to the smaller N’s in the younger group (the current indication for treatment with the RNS System has a minimum age of 18).

Across all patients, the median seizure reduction [25th–75th percentile] was 46.2 [15.8–74.6]% at the 2-year timepoint and 74.5 [46.5–97.4]% at the 9-year timepoint. To test whether the differences in the QoL and mood outcomes between the early and late treatment groups were related to differences in seizure outcomes, we also compared the QoL and mood outcomes in the early and late groups to changes in seizure rates (Supplementary Fig. 2). Across all patients, the percent change in seizure rate was linearly correlated with the change in QOLIE-31 summary scores at the 9-year time point (P < 0.01): patients with larger reductions in seizure rates also tended to have greater improvements in QoL. However, seizure rate reductions at 9 years did not significantly vary with epilepsy duration, and the distribution of seizure rate reductions...
did not differ between the early vs. late groups. For patients in the early treatment group who completed the QoL assessment at both timepoints \((N = 32)\), the median percent reduction in seizure rates was 77.0 \([28.5–100]\)% across 9 years, similar to the 74.5 \([39.2–96.1]\)% reduction in the late treatment patients \((N = 72)\). Similarly, patients in the early treatment group who completed the mood assessment at both time points \((N = 27)\) had a median mood score reduction of 49.8 \([2.7–78.4]\)% at 2 years, similar to the 55.0 \([16.3–76.7]\)% reduction in the late treatment group \((N = 70)\). Thus, the observed differences in QoL and mood between the early vs. late treatment groups do not appear to result from differences in seizure rate reductions.

4. Discussion

Patients treated with brain-responsive neurostimulation sooner following habitual seizure onset had significant improvements in multiple domains of QoL and in mood that were not observed in patients treated later in the course of their epilepsy despite similar treatment efficacy reducing seizure frequency. These results sug-
gest that earlier effective epilepsy treatment improves the opportunity for behavioral improvements, and that delayed treatment intervention, which is associated with similar seizure reduction benefit, results in more limited behavioral improvement. These results are consistent with the literature on QoL and mood changes following resective or ablative procedures [35–38]. These findings also underscore that improvements in QoL and mood are not restricted to patients who become seizure free; they are also evident in patients whose seizure frequency is reduced.

All RNS System trial patients were at least 18 years of age, and it is unclear whether similar results would be obtained in a younger population. It is possible that children would experience even larger improvements in epilepsy’s comorbidities than adults when treated with brain-responsive neurostimulation by reducing deleterious effects of seizures on psychosocial development [39]. Pediatric trials are needed to address these questions.

Perhaps surprisingly, the differences in QoL and mood in patients treated earlier vs. later were not accompanied by differences in seizure outcomes (Supplementary Fig. 2). Both groups experienced substantial reductions in seizure frequency, with a median percent reduction of 46.2 at 2 years of treatment and 74.5 at 9 years of treatment. Improvements in mood without improvements in seizure reduction have also been reported with vagus nerve stimulation (VNS) [40], suggesting a possible direct behavioral therapeutic benefit of stimulation, and in fact, VNS is an effective option for resistant epilepsy [41]. Future studies are needed to evaluate whether these findings are specific to particular brain networks.

This study has four key limitations. First, the analyses for this study were retrospective, and the original studies were not powered for some of the analyses of interest, such as differential effects with different stimulation sites. Second, the early and late treatment groups had different QoL and mood scores at baseline. Patients in the late group started out with higher QoL and lower depression than those in the early group, which may be partially accounted for by patients in the late group having had more time to adjust to life with epilepsy. Thus, greater improvements in mood and QoL in the early group may partially be attributable to their QoL and mood scores having more “room to improve” relative to baseline. Third, baseline QoL and mood scores could have been influenced by anxiety related to the upcoming surgical procedure. Fourth, patients who were treated later tended to be older, so it is not possible to rule out natural effects of aging on these comorbidities over time, which may have negatively affected the late group more than the early group. However, age of enrollment did not appear to explain differences in the two groups (Supplementary Fig. 1), which argues against this possibility.

Despite these caveats, this study provides further evidence that earlier epilepsy treatment that reduces seizure frequency increases the opportunity for QoL and mood improvements. These observations may extend to other forms of neuromodulation. For instance, changes in QOLIE-31 as well as subjective physician assessment of QoL have indicated that open-loop and cardiac-closed-loop VNS can improve QoL [42–44]. Improvements in long-term QOLIE-31 scores have also been observed with DBS for epilepsy [45]. Although the impact of the duration of epilepsy on DBS-related improvements in QoL has not yet been reported, Englot et al. [43] reported that a shorter time to VNS implantation was correlated with a larger improvement in QoL. Thus, the relationship between duration of epilepsy and improvements in QoL is likely not unique to brain-responsive neurostimulation. The current study adds to the growing body of evidence of the importance of minimizing the time to treatment for patients with medically refractory epilepsy, not only with resective or ablative procedures but also with neuromodulation.

These results underscore the importance of evaluating overall treatment effectiveness, which incorporates treatment effects on comorbidities into treatment outcomes, rather than simply characterizing treatment efficacy based upon changes in seizure frequency; in this cohort, favorable changes in behavioral comorbidities are not entirely dependent on seizure freedom. Uncontrolled epilepsy has a profound impact on life experience and self-identity; the patient’s experience of epilepsy’s mood and social comorbidities influences their chance for overall life improvement. Reducing seizures may not be sufficient for sustained improvements in QoL or mood in persons who have experienced nearly a lifetime of epilepsy, and who may not have enough time in their future for meaningful life change.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.107868.

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