**RNS—It Never Gets Old**

**Keywords**
Epilepsy, Neurostimulation, NeuroPace, RNS, LTT

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**Nine-Year Prospective Efficacy and Safety of Brain-Responsive Neurostimulation for Focal Epilepsy.**

Nair DR, Laxer KD, Weber PB, et al. Neurology. 2020;95(9):e1244-e1256. doi:10.1212/WNL.0000000000010154.

Objective: This commentary aims to prospectively evaluate safety and efficacy of brain-responsive neurostimulation in adults with medically intractable focal onset seizures (FOS) over 9 years. Methods: Adults treated with brain-responsive neurostimulation in 2-year feasibility or randomized controlled trials were enrolled in a long-term prospective open label trial (LTT) to assess safety, efficacy, and quality of life (QOL) over an additional 7 years. Safety was assessed as adverse events (AEs), efficacy as median percent change in seizure frequency and responder rate, and QOL with the Quality of Life in Epilepsy (QOLIE-89) Inventory. Results: Of 256 patients treated in the initial trials, 230 participated in the LTT. At 9 years, the median percent reduction in seizure frequency was 75% ($P < 0.0001$, Wilcoxon signed rank), the responder rate was 73%, and 35% had a ≥ 90% reduction in seizure frequency. We found that 18.4% (47 of 256) experienced ≥ 1 year of seizure freedom, with 62% (29 of 47) seizure-free at the last follow-up and an average seizure-free period of 3.2 years (range: 1.04-9.6 years). Overall QOL and epilepsy-targeted and cognitive domains of QOLIE-89 remained significantly improved ($P < 0.05$). There were no serious AEs related to stimulation, and the sudden unexplained death in epilepsy (SUDEP) rate was significantly lower than predefined comparators ($P < 0.05$, 1-tailed $\chi^2$). Conclusions: Adjunctive brain-responsive neurostimulation provides significant and sustained reductions in the frequency of FOS with improved QOL. Stimulation was well tolerated, implantation-related AEs were typical of other neurostimulation devices, and SUDEP rates were low.

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**Commentary**

The article “Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy” by Drs. Nair and the RNS System Long-Term Treatment (LTT) study group is the latest published outcome data for a population of 230 RNS patients followed over 9 years. The article is more of an update or progress report on how things are panning out for patients who have the RNS system; it allows people.

The paper describes earlier trials (which is useful):

1. The 65-patient feasibility trial,
2. The ensuant 191-patient randomized, pivotal, trial, and then
3. The LTT which has studied RNS patients for an additional 7 years prospectively (after the 2-year pivotal trial).

The LTT assessed safety, seizure frequency, and quality of life from 2004 to 2018. Finer details of the patients’ presentation, treatment armamentarium, and demographics are reported. They conclude that this report provides “Class IV evidence” that “brain-responsive neurostimulation is acceptably safe, reduces seizure frequency and improves quality of life (QOL).”

Results: of the 230 patients enrolled in the LTT, 162 completed the study. Patients who did not complete the LTT did so because of the following: (1) choosing to not replace the stimulator at the end of service point of the battery, (2) other treatment options, (3) insufficient efficacy, and other less prominent reasons.

The authors do address this issue by comparing the data at each time point from all patients who completed the trial (constant cohort) to a last observation carried forward (LOCF) analysis.
analysis supports that the clinical improvement over time was not directly due to enrichment in the patient population.

Median percent reduction in seizures at the end of 3 years was 58%. This improved steadily reaching 75% by the end of 9 years. 18.4% had at least 1 seizure-free interval of more than 12 months. QOLIE-89 scores improved consistently.

The authors also allude to potential cognitive changes (which turned out to be for the better over time in the LTT). The cognitive effects of closed-loop (RNS) vs open-loop stimulation (Medtronic anterior nucleus of the thalamus) is an area of active debate in this field. In the earlier blinded RNS study, there was no difference in the percentage of subjects in the treatment and sham groups experiencing adverse effects related to depression, suicidality, or memory function. Only 1 participant in the LTT reported a serious adverse event of new memory dysfunction. Depression and suicidality did not differ much from baseline. Device-related serious adverse events in the RNS was 4.1%. Other adverse events they report are infection (essentially always superficial) and SUDEP (reduced by approximately 1/3 from the expected rate for this population).

The summary is limited because it does not explain in sufficient detail how the RNS system behaves and is used in clinical practice. The manual for the RNS system states, “Note that the RNS® System is not a seizure detection device.” However, we in the RNS community do use the RNS system as a unique diagnostic tool via ambulatory electrocorticography to inform other treatment decisions. Clinicians use the trends in epileptiform activity recorded by the RNS to titrate anti-seizure medications (ASMs) and plan future surgeries—resection, laser ablation, and DBS). Only 22 of the 230 patients did not change anti-seizure medications during the LTT study. Thus, over 9 years, with objectively informed data (raw detection numbers but also surrogates of clinical seizures such as long episodes and amplifier saturations), clinicians adjusted ASMs, and tried other adjuvant therapies; as expected, these patients got better over time. Theoretically, some of the clinical improvement could have occurred as a result of more objective patient management (uniquely provided by the RNS) without any direct neurostimulation at all. With medication adjustment as a primary intervention, remission periods of 12 months or longer have been documented in 18% of patients with drug-resistant epilepsy by 5 years, and 33.4% by 7 years, only to subsequently recur in the majority of patients re-enforcing the conceptual distinction between intermittent seizure remission and sustained seizure freedom.

Clinical improvements published in the LTT occur in a context of multi-modality treatment—not just the RNS alone (the device as “single-modality” treatment). This is not emphasized in this paper. In fact, the complexity of changes in treatment over time (multi-modality treatment) makes one of their main claims unproven—“brain-responsive neurostimulation...reduces seizure frequency”—at least in this context.

Another feature of the RNS is that it is not a static device. It works because we learn how to ‘make it work’ over months to years. For an individual patient, over 9 years with ongoing adjustments of detection and stimulation settings, I expect that this cohort of patients would reap increasing benefits of the RNS. The steady improvements seen over 9 years of follow-up may be due to physiologic neuromodulation (the original paradigm) but, also important, may be due to our modulation, titration, and optimization of the device itself and its behavior.

In conclusion, people with drug-resistant epilepsy who are not candidates for traditional resective epilepsy surgery are in need of proven, effective, meaningful, and safe palliative options. Use of the RNS is associated with epilepsy that gets less and less severe over time—regardless of the many interacting mechanisms. Future rigorous, creative, and pioneering research will hopefully help us better identify its ideal applications, and how it works.

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