

SHORT RESEARCH ARTICLE

Practice trends and the outcome of neuromodulation therapies in epilepsy: A single-center study

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Abstract

Neuromodulation therapies (VNS, RNS, and DBS) can improve seizure control in persons with epilepsy. However, there is a significant service gap in integrating these therapies in clinical care. Our epilepsy center has established an epilepsy neuromodulation clinic to improve access to patients, communication with referring physicians, track outcome and train future providers in programming neuromodulation devices. We report the (a) treatment outcome of the available neuromodulation therapies (ie, reduction in seizure frequency over 6-12 months follow-up); and (b) demonstrate the benefit of the specialized clinic (rapid titration, continuity of care, superior access for patient and vendors). In this single-center, retrospective study, forty-three adults (VNS = 27; RNS = 16) with drug-resistant epilepsy were followed in the clinic during the 19 months study period. About 44-69% of patients reported > 60% decrease in seizure. All patients were scheduled in the clinic within 2-4 weeks, and stimulations were optimized rapidly. About 40% of patients participated in research while 28% were referred for additional diagnostic studies. Nineteen students and fellows were trained in programming neurostimulator. Epilepsy neuromodulation clinic can serve as an optimal solution for patients as well as providers due to rapid access, better continuity of care, higher recruitment for research studies, and training health professionals.

KEYWORDS

epilepsy, deep brain stimulation, responsive stimulation, vagal nerve stimulation

1 | INTRODUCTION

Despite advances in the medical and surgical management of epilepsy, a significant proportion of patients (approximately 15-40%) continue to suffer from seizures.¹ Poor seizure control has been associated with poor quality of life, depression, anxiety, and adverse side effects from medications.²

A growing body of evidence suggests that neuromodulation therapies complement other medical and surgical interventions to improve seizure control and cognition in persons with epilepsy (PWE).³⁻⁷ For example, the VNS provides reduction in seizure frequency over 50% in 60% of patients while the RNS provides 62% median reduction in seizure frequency over 3-5 years postimplantation. The DBS provides 70%

Jamy and Kaur authors contributed equally to this work

[Correction added on June 20, 2019, after first online publication: The Acknowledgment section has been updated.]

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median reduction in seizure frequency over 5 years. The Food and Drug Administration has approved three neuromodulation therapies for epilepsies—vagal nerve stimulation (VNS), responsive neurostimulation (RNS), and recently anterior thalamic deep brain stimulation (DBS). There is a significant challenge in integrating these neuromodulation therapies in clinical practice including appropriate patient selection, education for informed decision making, availability of trained physicians to implant the device safely, and programming or troubleshooting the device to optimize therapy.

Additionally, there is a knowledge gap in understanding the therapeutic effectiveness, practice variations, and long-term cognitive outcome with some of the newer approved therapies (like RNS and DBS). To meet these demands, our level-IV epilepsy center adopted an innovative approach by establishing an epilepsy neuromodulation clinic as a hub that offers a full array of services (clinical and translational research) and anchors a network of secondary establishments (spokes) distributed within the southeast (gulf coast) regions of United States of America. In this retrospective study, we report the practice trends and outcomes accomplished over a year in a highly specialized clinic. We report the followings: (a) treatment outcome of the available neuromodulation therapies (ie, reduction in seizure frequency from VNS and RNS); (b) demonstrate the benefit of the specialized clinic (rapid titration, better continuity of care, superior access for patient and vendors); (c) recruitment for research studies; and d) education and training outcome of future providers.

2 | METHODS

A single-center, retrospective study involving all adults followed in the neuromodulation clinic between January 1, 2017, and July 31, 2018. Their electronic medical records were reviewed, and the following data were collected: patient demographics, seizure characteristics, preimplant diagnostic tests, time from referral to implantation, stimulation titration schedule, seizure frequency pre- and postimplantation, and complications including stimulation-related side effects. The one half day clinic is lead by a board-certified fellowship trained epilepsy neurologist (SP) and is attended by a field engineer or a specialist in programming neurostimulator, rotating resident and fellow from neurology or neurosurgery, medical students, nurse practitioner, and other physicians who wished to gain experience in programming neurostimulators. Patients are followed-up every 1-4 month depending on the stimulation therapy (RNS or VNS or both). For patients with RNS, an example of a follow-up schedule: 2 weeks postimplant, thereafter every 4-6 weeks for next 2-3 visits and after that every 4 months. For patients with VNS, an example of a follow-up schedule: every 2-3 weeks postimplant for initial 4-6 visits where rapid up-titration was performed and after

that every 4 months. The primary outcome measures were as follows: (a) the percentage change from baseline seizure frequency at the 9-12 months follow-up; (b) time efficiency measured by the intervals between referral to implantation and between implantation to achieve optimum stimulation parameters. A reduction in self-reported seizures by >60% is considered a responder, <30% as a nonresponder and between 30-60% seizure reduction as the intermediate group.⁸ The optimum stimulation parameters for a patient were defined as the highest parameter that he/she can tolerate and that provided maximum seizure reduction. Therefore, in the clinic, we up-titrated the stimulation parameters until the patient reported seizure reduction >60% or had side effects that were intolerable. Secondary outcome measures were as follows: (a) some referrals for inpatient video EEG; (b) recruitment for research studies. The study has approval from the Institutional Review Board.

3 | RESULTS

3.1 | Population demographics

Twenty-seven subjects (mean 34.2 years; range 19-60 years) with VNS (Aspire® and SenTiva models) and 16 subjects (mean 38.18 years; range 28-58 years) with RNS were followed in the clinic during the study period (Table 1). The referral for managing VNS was within the state while RNS included in-and-out -of state (Figure 1A,C). Within the RNS cohort, three patients had prior VNS that was deactivated, and only one subject had concurrent VNS and RNS therapies. At the time of this manuscript, three additional subjects were recruited and waiting for the anterior thalamic DBS.

3.2 | The outcome of VNS

Seven subjects had drug-resistant generalized epilepsy while the remaining subjects (N = 20) had multifocal epilepsy (Table 1A). Three patients had prior epilepsy resective surgery. Four subjects had a profound intellectual impairment, and their mobility was restricted to a wheelchair. Of the 27 subjects, seven (25%) had a new implant while 13 (49%) had renewed their battery within the study period. At the last follow-up (>8 months), 44% (N = 12) self-reported >60% reduction in seizures, while 15% (N = 4) were nonresponders. None were seizure free (Figure 1D). Auto-stim features (automated triggered stimulation based on increased heart rate) were used in therapy in four subjects. The most tolerated stimulation current ranged between 1.5-2.25 mA, and this was achieved within 8-13 weeks. Eleven (41%) had reported increased cough and hoarseness of voice which were transient. Only one patient had symptomatic partial vocal cord paralysis that was attributed to chronic VNS stimulation and the device was switched off.

TABLE 1 Demographics and clinical details of patients with implanted VNS (A) and RNS(B)

(A) Total patients VNS	27
Mean age (y)	34.2 (R = 19-60)
Female	10
Epilepsy types	
Generalized	7
Focal/ multi focal	20
Mental retardation	
Profound (IQ < 25)	4
Severe (IQ 25-40)	3
Moderate (IQ 40-55)	8
Mean Anti epileptic drugs	
Baseline	3.1 (R = 2-6)
At last follow-up	3.2 (R = 2-6)
Previous resective surgery	3
Median age of implant (y)	19 (R = 11-36)
Median duration of implant (y)	6(R = 1.5-24)
(B) Total patients RNS	16
Mean age (y)	38.8 (R = 28-58)
Female	7
Epilepsy localization	
Bi mesial temporal	5
Dominant temporal	8
Eloquent cortex (sensory motor, Broca's)	3
Mean Anti epileptic drugs	
Baseline	3.28(R = 2-5)
At last follow-up	3.3 (R = 2-5)
Previous resective surgery	6

Abbreviation: R, range; RNS, responsive neurostimulation; VNS, vagal nerve stimulation.

3.3 | The outcome of RNS

Six patients had prior resection before implantation of RNS (Table 1B). Implantations were bilateral hippocampal (N = 5), unilateral temporal (N = 8), and fronto-parietal (N = 3). The mean duration of epilepsy before implantation was 24.4 years (range 12-39 years). At the last follow-up (>8 months), 69% (N = 11) self-reported >60% reduction in seizures, while 6% (N = 1) had < 30% decrease in seizure. 25% (N = 4) was seizure-free (Figure 1D). One patient with bilateral hippocampal RNS had probable SUDEP (Sudden Unexpected death in epilepsy).⁹ The patient reported an initial decrease in seizure severity but later had increased bilateral tonic-clonic seizures preceding death. One patient reported transient eye and face twitching with ipsilateral hippocampal RNS depth electrode stimulation. The symptoms resolved following decreasing stimulation current.

3.4 | Continuity of care and access to the clinic

All patients with a new VNS implant (N = 7) underwent a rapid titration schedule and were followed bi-weekly for the first 3-4 months. All except one had their VNS implanted within six weeks after referral (range 2.5-13 weeks). The delay in scheduling implantation for one subject was related to finances and other logistic issues due to transportation from a group home. After implantation, all patients were followed in the special clinic within three weeks (Figure 1B). Regarding RNS, the follow-up was initially every 4-6 weeks for the first three months and after that spaced out to once every 3-4 months. Of the five patients who were from out of states, four continued to follow in our clinic regularly while one patient attended the clinic annually. There was no loss to follow-up during the study period. Seven subjects (N = 5 for VNS) requested urgent titration of stimulation due to side effects, and this was achieved within three weeks. The side effects included increased cough, palpitation, and hoarseness of voice.

3.5 | Referral for inpatient diagnostic tests to optimize therapy

Of 43 patients who were followed in our special clinic, 28% (N = 12) were referred for inpatient video EEG monitoring. Reasons for the diagnostic study included referral for potential epilepsy surgery (N = 4 in patients with VNS implanted in another facility), diagnostic clarification before VNS implantation (N = 3), the discrepancy in seizure count between self-reported and detected in RNS (N = 3) and to confirm atypical spell (N = 2).

3.6 | Participation in research and education

40% (N = 17) patients from the neuromodulation clinic participated in other prospective studies (N = 5 in the state-sponsored cannabidiol oil therapy,¹⁰ N = 8 in the company sponsored (Neuropace) observational study, N = 4 in validating seizure warning watch study) (Figure 1E). Over the last 1.5 years, three nurse practitioners, six residents (combined neurology and neurosurgery), two epilepsy fellows, five engineering students, and three medical students rotated in the clinic and learned about the devices (Figure 1F,G).

4 | DISCUSSION

Over the year's research and technological advancements have resulted in the approval of two additional neuromodulation therapies (RNS, DBS) that are effective in controlling seizures in a significant cohort where seizure outcome was suboptimal.^{3,5,7} The challenge ahead of us is to integrate

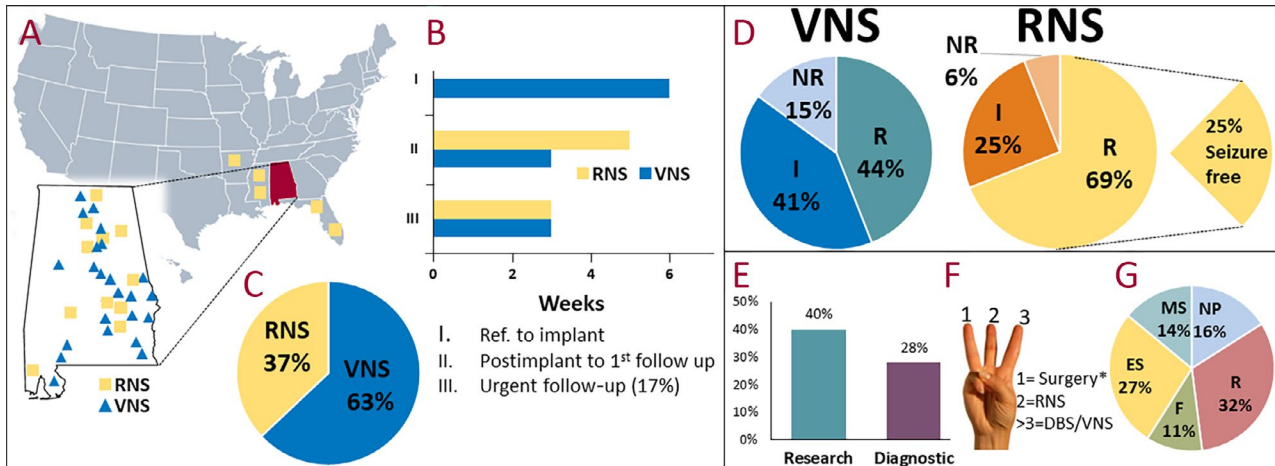


FIGURE 1 A, Referral sites for vagal nerve stimulation (VNS—marked triangle) and responsive neurostimulation (RNS—marked square). The epilepsy neuromodulation clinic is located in Birmingham, Alabama. Note the out of state referral for RNS from Mississippi (N = 2), Arkansas (N = 1), Florida (N = 2). B, Horizontal bar plots with X-axis representing weeks to access for care: I—from referral to implantation of VNS; II—from implantation (VNS, RNS) to first clinic appointment; III—Urgent follow-up to manage stimulation (VNS, RNS) related side effects. C, Distribution of patients followed in the clinic with VNS (N = 27) and RNS (N = 16). D, Percentage of patients with seizure outcomes classified as R = Responder; NR = Nonresponder; and I—Intermediate between R and NR. E, Percentage of patients recruited in research and diagnostic studies. F, Example of an educational material used to teach the criteria for selecting appropriate neuromodulation therapies. If the seizure focus can be localized by one finger then consider epilepsy surgery, two fingers then consider RNS, three or more fingers then consider thalamic DBS or VNS. *RNS is preferred over resection if eloquent cortex overlaps seizure focus. G, Percentage of healthcare professionals trained in the clinic. MS, medical students; NP, nurse practitioner; ES, engineering students, neurology and neurosurgery residents (R) and fellows (F).

these different therapies in busy clinical practice. Here, we have demonstrated the value of organizing a specialized clinic with a focus on rapid accessibility. Having a specialized neuromodulation clinic allows efficient management of resources like scheduling field engineers to attend the clinic and to avoid multiple visits within a week. Also, one important aspect of titrating stimulation is patient tolerability, and the clinic provided rapid access within three weeks to manage stimulation-related side effects.¹¹

Additionally, physicians, nurse practitioners (NPs), and physician assistants (PAs) can work in teams to deliver care in ambulatory settings.^{12,13} Different models of practice can be trialed and adopted for the efficient management of the neuromodulation clinic. For example, an NP can be trained in neuromodulation and can coordinate with multiple epileptologist and field engineers to deliver care. One advantage of such a model is the continuity of care by the patient's epileptologists. Future studies are needed to compare the variations in practices between centers and how this relates to outcome measures. However, setting up a special clinic has its challenges. In a busy tertiary academic center, mobilizing resources (like availability of clinic room, certified medical assistants, scheduler) can be challenging and requires support from the administrative and financial managers. Transportation for frequent and multiple follow-up can be challenging for patients and their caregivers who live hours away from the clinic.

The study has limitations. The outcome of neuromodulation may be confounded by titration of medications that was performed by the referring physician. Five patients participated in the state-sponsored cannabidiol oil therapy, and this could have confounded the seizure outcome. A smaller cohort and shorter duration of follow-up was another limitation of the study. Within that limitation, the seizure outcome for VNS and RNS was comparable to published studies.^{3,7} Beyond the seizure outcome, the study demonstrated the success of a model that integrates service with business, teaching, and research. Interestingly, to our knowledge, this is the first study to report the outcome of two neuromodulation therapies (RNS and VNS) in patients with drug-resistant epilepsies who are managed by a single physician. The cohorts with implanted VNS are different from RNS in multiple ways including the presence of a higher learning disability, having generalized or a widespread network disease. Therefore, as anticipated seizure freedom from neuromodulation therapy was seen only in patients with RNS (25% in this study) and the overall responder's rate were different (VNS 44% vs. RNS 69%). At present, neuromodulation therapies are offered only when resection failed to control seizures or seizure foci cannot be resected. Therefore, both VNS and RNS are considered palliative therapies although a significant reduction in seizures, SUDEP (Sudden Unexpected Death in Epilepsy), and improved quality of life can be obtained with these therapies.^{3,7,14,15}

5 | CONCLUSION

Epilepsy neuromodulation clinic can serve as an optimal solution for patients as well as providers due to rapid access, continuity of care, and prompt follow-up appointments. Physicians can closely monitor the patient's clinical course and recruit appropriate patients for clinical trials to advance science, and use this clinic as a resource to educate and train future specialist related to this field.

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CONFLICT OF INTEREST

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