

# Neuromodulation and Epilepsy

From the vagal nerve to the deep brain, neuromodulation provides another treatment option for patients with epilepsy.

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Neuromodulation—implantation of an electrode along the neural axis and an impulse generator (IPG) that sends an electric signal back to the brain to disrupt epileptic networks—continues to grow in application and technology. In some cases, the IPG not only sends impulses to the brain, but also senses impulses from the nervous system. Mechanisms of action for neuromodulation therapies are as yet unknown as are many etiologies of the different epilepsies.



There are 3 neuromodulation therapies approved by the Food and Drug Administration (FDA) for treating patients with drug- or treatment-refractory epilepsy: responsive neurostimulation (RNS) (NeuroPace, Mountain View, CA), vagal nerve stimulation (VNS) (LivaNova, London, England), and deep brain stimulation (DBS) (Medtronic, Dublin, Ireland). The chief advantage of neuromodulation is that it does not involve removing or lesioning brain tissue and the physician can titrate electric therapy akin to managing medication dosage.

We review randomized clinical trial (RCT) data on the 3 FDA-approved neuromodulation therapies for treating patients with drug-refractory epilepsy. A brief overview is in the Table.

## Responsive Neurostimulation Device and Technique

In RNS, a device that delivers electric stimulation to a target brain region via surgical implantation on the brain surface (ie, subdural) or within deep brain structures is combined with an active device consisting of a battery and circuit board that are recessed within a ferrule implanted into the cranium under the scalp.<sup>8</sup> The electrodes are implanted into a brain region hypothesized to correspond to an epileptic onset or spread zone and serve a dual function of recording electrocorticography and delivering stimulation.

Electrocorticographic recordings are transferred to the built-in computer chip, which analyzes the signal and can be programmed to detect events that could correspond with seizure onset. The system can store some EEG data that can also be transferred via a wand and external laptop computer. This allows the neurologist to interpret the electrocorticogra-

TABLE. INDICATIONS AND EFFICACY OF NEUROSTIMULATION TECHNIQUES

	Patient factors	Seizure types	Seizure frequency reduction in 3 mos blinded period	Seizure frequency reduction in open-label extensions
RNS <sup>1,2</sup>	Age ≥18 y Refractory to ≥2 AEDs ≥3 seizures/month for ≥least 3 mos	Partial onset with 1-2 foci Frequent disabling seizures Focal seizures with impaired awareness Focal to bilateral tonic-clonic seizures	37.9%	44% mean (1 y) 53% mean (2 y) 66% achieve > 50% (8 y)
ANT DBS <sup>3,4</sup>	Age >18 y Seizures >6/month Refractory to >3 AEDs and taking 1-4 drugs	Partial or secondarily generalized	40.4%	41% mean (1 y) 56% mean (2 y)
VNS <sup>5-7</sup>	Age ≥4 y	Partial onset seizures	15% to 28%	22.5% achieve ≥ 90% 40.5% achieve ≥ 75% 63.75% achieve ≥ 50% 36.25% achieve < 50%

Abbreviations. AED, antiepileptic drugs; ANT, anterior thalamic nuclei; DBS, deep brain stimulation; RNS, responsive neurostimulation; VNS, vagal nerve stimulation.

phy. This system is considered a closed-loop device that can be programmed to detect events and then deliver electric stimulation when an event is detected. It is described as similar to a cardiac pacemaker that controls abnormal cardiac electric discharges.<sup>8</sup> RNS is most effective when 1 to 2 apparently isolated seizure foci correspond to a well-localized onset zone.<sup>9</sup>

### Indications

Before implantation there should be a clear hypothesis localizing seizure onset to 1 or 2 foci. Electrodes should be implanted to identify seizure events and then placed for strategic disruption of seizure onset or propagation. Work-up of a patient considering RNS may include MRI, positron-emission tomography (PET), magnetic electroencephalography (MEG), single-photon emission computed tomography (SPECT), and sometimes invasive implantation with grid, strip, or stereoEEG electrodes. Most commonly, RNS has been used in patients with bilateral temporal seizure onset, seizure onset in eloquent or nonresectable brain regions, contralateral temporal regions, and in whom seizures are persistent or responded suboptimally to surgical intervention or VNS. There are other described cases where RNS has also been successful.

### Safety and Efficacy

The safety and efficacy of RNS was established in a multicenter, double-blind, RCT of 191 patients with refractory focal seizures with or without secondary generalization.<sup>10</sup> Of those enrolled, 32% had prior epilepsy surgery and 34% previously had VNS, which was turned off or explanted before enrollment. Patients were randomly assigned to activated and nonactivated groups, and all had the RNS implantation procedure. After a 4-week period during which no patients' systems were activated to control for any temporary insertion effect, those in the activated group had RNS activated for 12 weeks. Those in the nonactivated group served as controls in the blinded portion of this trial. After the initial 12 weeks all patients' systems were activated, and patients were followed on an open-label basis. Both groups had an overall 20% reduction in seizure frequency reduction.<sup>10</sup>

In the blinded phase, the activated stimulation group had a statistically significant 37.9% reduction in seizure frequency compared with the 17.3% reduction of the control group.<sup>1</sup> These results are close to the control trial of DBS in anterior thalamic nuclei (ANT).<sup>11</sup> There were no significant changes in neuropsychologic status during the blinded or open-label periods.<sup>10</sup> Further long-term follow-up showed median 44% reduction in seizure frequency at 1 year and 53% at 2 years; 20% of patients had seizure freedom for at least 6 months.<sup>2,12</sup>

In ongoing follow up over 8 years, 66% of patients enrolled in the trial achieved >50% seizure reduction at year 8, 30% had >90% seizure reduction over the most recent 3 months, and 29% had  $\geq 1$  period of more than 6 months without seizures.<sup>2</sup>

### Advantages

In RNS a particular epileptogenic region in the brain is targeted and electric stimulation is intermittently triggered and delivered in response to detected events.<sup>3</sup> Long-term follow-up shows RNS can provide meaningful results for patients with treatment-resistant epilepsy. NonRCT data suggests 14% to 15% of patients may experience seizure-free periods of 1 year with RNS.<sup>13,14</sup> Many patients with RNS also experience improvement in neuropsychologic measures including naming, verbal memory, visual memory, and executive function.<sup>14</sup> There is also a study describing reduced rates of sudden unexpected death from epilepsy (SUDEP) in patients treated with RNS.<sup>14</sup>

### Disadvantages and Adverse Effects

Patients with RNS implanted cannot undergo MRI.<sup>16</sup> Adverse events include a 2.6% infection rate and an intracranial hemorrhage rate of 2.1%. The adverse events related to implantation were not higher than what had been reported in previous surgical neuromodulation trials for adjunctive treatment of partial-onset seizures.<sup>2</sup>

## Deep Brain Stimulation

### Device and Technique

In DBS, 2 depth electrodes with 4 contact points specifically designed for long-term implantation are placed within the brain parenchyma in a neural target. The wires are anchored to the skull. Through a separate incision, wires are connected to a thicker wire, termed the *extension* that is carefully tunneled under the skin, exiting through a second incision, usually in the subclavicular region. Here the wires are connected to a battery or IPG. Incisions used for DBS are typically smaller than in RNS; recovery is somewhat easier compared with RNS.

DBS delivers a continuous or cycled electric signal to the brain and is an open-loop system, meaning stimulation is not triggered by seizure detection. Patients with DBS can undergo MRI in certain conditions. Many DBS targets have been explored including ANT, nucleus accumbens (NA), hippocampus, cerebellum, substantia nigra, caudate nucleus, subthalamic nucleus (STN), and motor cortex.<sup>17-19</sup> Most targets have not been tested in RCTs. We review the 3 targets with the most evidence available.

### Deep Brain Stimulation at Anterior Nuclei of Thalamus

*Safety and Efficacy.* The ANT projects to the cingulate cortex, amygdala, hippocampus, orbitofrontal cortex, and caudate where it may influence focal seizures and seizure propagation. Multiple pilot case series have shown benefit of ANT neurostimulation for patients with epilepsy.<sup>17,19-23</sup>

In a large-scale multicenter, double-blind, RCT of bilateral ANT stimulation, 110 patients with medically refractory par-

tial seizures, including secondarily generalized seizures were randomly assigned to treatment and control groups.<sup>11</sup> The device was not activated for the first month after surgery for both groups, then only the treatment group had their devices activated for 12 weeks, after which time all patients had stimulation. In the double-blind phase, the activated group had a median 40.4% seizure reduction rate vs 14.5% seen in the control group. Long-term follow-up showed a seizure reduction rate of 41% at 1 year and 69% at 5 years. At 1 year, 43% of patients had achieved  $\geq 50\%$  reduction in seizure frequency, which rose to 68% at year 5. After 5 years, 11 patients were seizure free during the last 6 months of follow-up.<sup>24,25</sup>

This study led to approval of ANT DBS as an adjunctive therapy for patients with epilepsy first in Europe, Canada, Australia, and then the US by the FDA on April 27, 2018<sup>26</sup> for refractory epilepsy characterized by focal seizures, with or without secondary generalization in patient age 18 years or more.<sup>3</sup>

### Advantages

With the current DBS system, a patient with the device can conditionally undergo MRI if needed. Many patients with multifocal nonlocalized epilepsy will be better candidates for ANT DBS compared with RNS in which a zone of onset with 1 to 2 foci is indicated. It is not yet known whether cyclic stimulation or intermittent responsive stimulation is superior.

### Disadvantages and Adverse Effects

The rate of adverse effects seen in DBS for patients with epilepsy seems to be similar to that seen in other uses of DBS. The most common device-related adverse effects were paresthesias (18.2%), implant site pain (10.9%), and infection (12.7% over the course of the entire study period). There were no symptomatic hemorrhages although 4.5% of patients had incidental hemorrhages on neuroimaging.<sup>24</sup> New types of seizures were seen in 7 treated patients; 3 treated patients and 2 control subjects experienced status epilepticus. During the study, 7 patients died from SUDEP that was not device related according to the investigator monitoring committee; this rate is lower than that seen in the general population of patients with drug-resistant epilepsy. Depression occurred in 8 treated patients and in 1 patient from the control group, and memory loss was more frequent in the stimulated group (7 treated patients and 1 from the control group.)<sup>11,24</sup>

### Deep Brain Stimulation at Hippocampus

Both DBS and RNS have used the hippocampus as a neurostimulation target for patients with epilepsy. Several small prospective studies have been attempted in a few patients which are highlighted below.<sup>27-30</sup> There is great interest in the hippocampus as a potential target for neurostimulation because of its role in the temporal epileptic circuit.

A double-blind, randomized, controlled, cross-over trial test-

ed efficacy of hippocampal DBS in 2 patients.<sup>28</sup> Neither patient was a good candidate for open surgery because they had seizures arising from independent bitemporal foci; 1 patient had a normal MRI and the other had mesial temporal sclerosis (MTS). During 3 months of neurostimulation there was a 33% reduction in seizure frequency for both patients, and after the device was deactivated, both had a persistent 25% reduction in seizure frequency for an additional 3 months after the device was deactivated. There were no serious adverse events reported and no subjective adverse effect on memory and emotion; visuospatial memory deteriorated in 1 patient during the stimulation. A double-blind study of 9 patients with long follow-up range of 18 months to 7 years showed the rate of seizure reduction in patients receiving hippocampal DBS improved during longer follow-up without any neuropsychologic deterioration.<sup>29</sup> In another study, 3 patients with nonlesional refractory mesial temporal lobe epilepsy received hippocampal DBS and were followed for a mean of 34.7 months. This study reported a 93% reduction in seizure frequency with no neuropsychologic deterioration and complete disappearance of generalized tonic-clonic seizures.<sup>30</sup>

### Deep Brain Stimulation at Nucleus Accumbens

A randomized case series has been reported in which DBS electrodes were implanted bilaterally into both the NA and ANT in 4 patients with disabling seizures.<sup>31</sup> Stimulation of the NA resulted in a 50% or more reduction in frequency of disabling seizures in 3 of 4 patients after 3 months. Subsequently all 4 patients received ANT stimulation and no further improvement was seen. There was no neuropsychologic deterioration. This small study suggests NA stimulation is safe and may have efficacy, although further substantiation by a large-scale multicenter randomized controlled trial study is needed.

### Vagal Nerve Stimulation

#### Device and Technique

The FDA approved VNS in July 1997 for patients with drug-resistant seizures. The device has since been modified to increase battery life and provide some responsive stimulation. Adjunctive treatment of patients with partial onset seizures who are age 4 years and up is also FDA-approved.<sup>5</sup> Implanting VNS requires 2 incisions, first in the neck through which a triple-helical coiled lead is implanted onto the vagus nerve and second, where the lead is connected to an IPG. The newest version of the IPG includes a cardiac sensor that can deliver additional stimulation if tachycardia is detected. Surgical implantation of VNS is done under general anesthesia and takes approximately 2 hours.<sup>32</sup>

#### Safety and Efficacy

Open-label data from a retrospective review of 436 patients with treatment-refractory epilepsy who had VNS over peri-

ods of 10 days to 11 years (mean 4.94 years) show a mean 55.8% reduction in seizure frequency after VNS. Long-term seizure control from this review are in the Table. In addition to seizure control, long-term outcomes for patients with epilepsy treated with VNS include positive effects on mood, memory improvements, and a decrease in depressive symptoms.<sup>33</sup>

### Advantages and Disadvantages

The extracranial approach of VNS is safer than implantation of DBS or RNS. Patients may undergo conditional MRI. Some risks of VNS are infection, asystole, bradycardia, vocal cord paralysis, sleep apnea, and damage to the vagus nerve. Clinical trials and real-world experience show that VNS is safe and effective in controlling treatment-refractory epilepsy.

### Conclusion

Neurostimulation is effective in reducing seizure frequency and each of the 3 approved types is useful in select patient populations. Some types of neurostimulation have other beneficial effects on cognition and mood, and possibly reduced mortality. Neurostimulation provides palliative seizure reduction and is not a substitute for patients who are candidates for potentially curative surgical resection.<sup>25</sup> Questions remain, including the optimal stimulation parameters and how these may vary depending on the individual patient.

Although RNS detects EEG markers for seizures, this therapy may actually provide more stimulation than required, which raises the question of whether the efficacy of selective stimulation is because of action on a seizure focus, as expected, or by a long-term neuromodulatory effect of repeated stimulation.

In practice, neurostimulation approaches all have comparable therapeutic outcomes in reduction of seizure frequency that improves with the length of therapy. Choosing among VNS, RNS, and DBS depends primarily on the nature of the seizure. When there are well localized and not more than 2 seizure foci RNS is a good option. In a case of nonlocalizing or poorly localizing seizures there is good evidence for ANT DBS. In cases of multifocal epilepsy VNS is a good choice. Other patient factors and advantages and disadvantages of each therapy described herein should also be considered when choosing among neurostimulation therapies. ■

- Food and Drug Administration. Premarket approval (PMA) for neupace RNS system. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P100026>. Updated September 10, 2018. Accessed September 14, 2018.
- 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(3):432-441.
- Food and Drug Administration. Premarket approval (PMA) for Medtronic DBS therapy for epilepsy. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P9600095219>. Updated September 10, 2018. Accessed September 14, 2018.
- Carlson C. Epilepsy treatment stimulus package? Deep brain stimulation in treatment-resistant focal epilepsy. *Epilepsy Curr*. 2010;6(6):150-152.
- Food and Drug Administration. Premarket approval (PMA) for VNS Therapy System. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P9700035207>. Updated September 10, 2018. Accessed September 14, 2018.
- Elliot R et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav*. 2011;20(1):57-63.
- Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures—a randomized active-control trial. *Neurology*. 1998;51:48-55. 8. Wu C. Neuromodulation: closed-loop stimulation for epilepsy. International Neuromodulation Society. [https://www.neuromodulation.com/fact\\_sheet\\_epilepsy](https://www.neuromodulation.com/fact_sheet_epilepsy). Published January 5, 2018. Updated July 25, 2018. Accessed September 14, 2018.

- 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(3):432-441.
- Morrell MJ. RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011;77(13):1295-1304.
- Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51(5):899-908.
- 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(6):1005-1014.
- Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia*. 2017;58(6):994-1004.
- Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia*. 2015;56(11):1836-1844.
- Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. *Epilepsia*. 2018;59(3):555-561.
- Neuropace. RNS System Clinical Summary. <https://www.neuropace.com/manuals/ClinicalSummary.pdf>. Updated September 2017. Access September 14, 2018.
- Nagel SJ, Najm IM. Deep brain stimulation for epilepsy. *Neuromodulation*. 2009;12(4):270-279.
- Eisevich K1, Jenrow K, Schuh L, Smith B. Long-term electrical stimulation-induced inhibition of partial epilepsy. *J Neurosurg*. 2006;105(6):894-7.
- Klingner NV, Mittal S. Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy. *Clin NeuroNeurosurg*. 2016;140:11-25.
- Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. *Nat Rev Neurol*. 2014;10(5):261-270.
- Upton AR, Cooper IS, Springman M, Amin I. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. *Int J Neurol*. 1985-1986;19-20:223-30.
- Krishna V, King NK, Sammartino F, et al. Anterior nucleus deep brain stimulation for refractory epilepsy: insights into patterns of seizure control and efficacious target. *Neurosurgery*. 2016;78(6):802-811.
- Lin Y, Wang Y. Neurostimulation as a promising epilepsy therapy. *Epilepsia Open*. 2017;2(4):371-387.
- Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015;84(10):1017-1025.
- Schulze-Bonhage A. Long-term outcome in neurostimulation of epilepsy. *Epilepsy Behav*. 2018. Published online July 2, 2018. doi.org/10.1016/j.yebeh.2018.06.011. Accessed September 14, 2018.
- Peña C. Medtronic DBS therapy for epilepsy. Food and Drug Administration. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P9600095219a.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P9600095219a.pdf). Published April 18, 2018. Accessed September 14, 2018.
- Cukiert A, Cukiert CM, Burattini JA, Lima AM. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. *Seizure*. 2014;23(1):6-9.
- McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. *Epilepsia*. 2010;51(2):304-307.
- Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia*. 2007;48(10):1895-1903.
- Jin H, Li W, Dong C, et al. Hippocampal deep brain stimulation in nonlesional refractory mesial temporal lobe epilepsy. *Seizure*. 2016;37(348):1-7.
- Kowski AB, Voges J, Heinze HJ, et al. Nucleus accumbens stimulation in partial epilepsy - a randomized controlled case series. *Epilepsia*. 2015;56(6):e78-e82.
- Manuscript A, Stimulation VN. NIH Public Access. *Cogn Behav Neural*. 2015;1(2):64-73.
- Yamamoto T. Vagus nerve stimulation therapy: indications, programming, and outcomes. *Neural Med Chir (Tokyo)*. 2015;55(5):407-415.

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