Comparison of seizure control outcomes and the safety of vagus nerve, thalamic deep brain, and responsive neurostimulation: evidence from randomized controlled trials

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Epilepsy affects nearly 1 in 100 people, leading to substantial morbidity, mortality, and economic burden.\textsuperscript{2,17,18} Up to one-third of these patients are not helped by antiepileptic medications.\textsuperscript{17,18} For patients with medically refractory epilepsy, a potentially curative option is resection of the epileptic foci when they can be clearly delineated and safely resected.\textsuperscript{27} However, many patients are not suitable candidates for resection, and morbidity exists for surgery.\textsuperscript{3,16} Because of this, there is a substantial need for additional treatment modalities.

Electrical stimulation of the nervous system is a rapidly evolving treatment for refractory epilepsy, offering a reversible, adjunctive therapeutic option for patients who are otherwise not surgical candidates. Therapeutic stimulation can occur directly via DBS or indirectly via stimulation of peripheral nerves. Three modalities of stimulation now have Class I evidence supporting their use: VNS, DBS of the ANT, and RNS. This review will examine the evidence for each treatment modality and delineate which sets of patients might benefit most from each.

**Vagus Nerve Stimulation**

The VNS modality is the only US FDA– and CE Mark–approved stimulation therapy for epilepsy. The device consists of pliable, spiral-shaped electrodes that wrap around the vagus nerve and an IPG that is implanted below the clavicle and connected to the electrodes with subcutaneously tunneled wires (Fig. 1).\textsuperscript{10} The left vagus nerve is typically used due to concerns about inducing bradycardia or other arrhythmias when stimulating the right vagus, although recently reports of successful right-sided VNS have been published.\textsuperscript{22}

The vagus nerve is largely afferent (approximately 80%) and is composed predominantly of unmyelinated C fibers.\textsuperscript{10} These fibers project to the nucleus tractus solitarius in the brainstem, which in turn projects widely to other areas within the brainstem and to the cortex. It is presumably by these broad neuromodulatory influences that VNS exerts its antiseizure effect. Nevertheless, the exact mechanism by which VNS reduces seizure frequency is unknown, although studies have implicated a variety of neurotransmitters, such as noradrenaline\textsuperscript{15} and g-aminobutyric acid.\textsuperscript{1}

Abbreviations used in this paper: AED = antiepileptic drug; ANT = anterior nucleus of the thalamus; CE = Conformité Européenne; DBS = deep brain stimulation; IPG = implantable pulse generator; RNS = responsive neurostimulation; SANTE = stimulation of the anterior nucleus of the thalamus for epilepsy; VNS = vagus nerve stimulation.
wrapped around the left vagus nerve within the neck.

VNS system, with the IPG in the left chest, and the cuff electrode

“high”) or an active, low-frequency control VNS (denoted “low”) (Fig. 2). The patients remained on AEDs throughout the trial. High VNS consisted of a 20- to 50-Hz stimulation frequency, “on” times of 30–90 seconds, “off” times of 5–10 minutes, and the ability to activate the VNS system manually with an external magnet. The low VNS (control) group had stimulation frequencies of 1–2 Hz, “on” times of 30 seconds, “off” times of 1–3 hours, and no ability to activate the device manually.

After approximately 3 months of treatment (12–16 weeks), both trials showed significant reductions in seizure frequency compared with patient baselines (24.5% and 27.9%, respectively; Table 1). This is compared with the low-stimulation groups, which had reductions of 6.1% and 15.2%, respectively. The proportion of patients experiencing a reduction of ≥ 50% in their seizures at this same 3-month time point was between 23.4% and 31% (Table 1), again compared with 13% and 15.7% in the low-stimulation groups, respectively.

The inclusion criteria were similar between the 2 trials. Both required patients to have ≥ 6 seizures per month, be ≥ 12 years old, use at most 3 AEDs, and have medically refractory seizures. The EO3 trial, however, required seizures to be “predominantly partial,” whereas EO5 required that the 6 minimum seizures all be partial, but permitted other seizure types in excess of the minimum. The EO5 trial also added an upper age limit of 65 years, limited time between seizures to a maximum of 21 days, and required that AEDs be at steady state before the patient’s induction into the trial.

Adverse events were common in both high- and low-stimulation groups, although only voice alteration and dyspnea were significantly increased in the high versus low groups. Overall, 66.3% of actively treated patients experienced voice alteration; 45.3% had cough; 34.7% had pharyngitis; 28.4% had pain; 25.3% had dyspnea; 24.2% had headache; 17.9% had dyspnea, vomiting, and paresthesias; 14.7% had nausea; 12.6% had accidental injury; and 11.6% had fever and infection (Table 2).

Both Class I trials were short term, lasting only 12–16 weeks. After the trials were unblinded, the patients were continually followed, and the results seemed to improve over time. After 1 year, for example, patients in the EOS study experienced a 45% reduction in seizure frequency, and 35% had a reduction of ≥ 50% in seizures. In the EO5 trial, those patients who were randomized initially to high stimulation had a reduction of 43.0%, whereas those switched from low to high stimulation experienced a 27.5% reduction. Nevertheless, these unblinded extensions do not constitute Class I evidence.

Anterior Nucleus Stimulation

The ANT projects to both the frontal and temporal lobes and is part of the classic circuit of Papez. Because of this integral role in the limbic system, an area intimately associated with epilepsy, many groups have attempted stimulating the anterior nucleus in humans in an effort to suppress seizures, with varying degrees of success.

The SANTE trial (ClinicalTrials.gov NCT00101933) was a double-blind, randomized, prospective clinical trial of DBS of the ANT. It began in 2005, and results were published in 2010. It was sponsored by Medtronic, Inc. After accruing patients and determining their baselines for 3 months, all patients were implanted with a Model 7428 Kinetra Neurostimulator and Model 3387 DBS leads (both from Medtronic) (Figs. 3 and 4). One month after implantation, patients were randomized to active treatment, with stimulation parameters of 5-V pulses at 145 Hz, with 1 minute “on” and 5 minutes “off,” versus 0-V pulses with identical frequency and duty cycle in the control group (Fig. 2).

Inclusion criteria for the SANTE trial were similar to the VNS trials that preceded it: age range 18–65 years, partial seizures, ≥ 6 seizures per month, and medically refractory epilepsy (defined as at least 3 failed AEDs). Important differences are the minimum age of 18 years, rather than 12 years used in the VNS trials, and a maximum of 4 AEDs used concurrently at baseline (compared with 3 in the VNS trials). The SANTE trial also excluded patients with > 10 seizures per day and patients with brain tumors, neurodegenerative diseases, psychogenic seizures, or IQ < 70. If the prospective SANTE patients had VNS devices, these were removed at the time of DBS implantation.

After a follow-up of 3 months, treated patients had a median decrease in seizures of 40.4%, compared with 14.5% in the control group. As with the VNS patients, the SANTE patients were then unblinded and followed for an additional time period. After 2 years, the treated SANTE patients (in this unblinded cohort) had a 56% median reduction in seizure frequency, and 54% of patients had a reduction in seizures of ≥ 50% (Table 1).

Fig. 1. Implanted VNS. This chest radiograph shows an implanted VNS system, with the IPG in the left chest, and the cuff electrode wrapped around the left vagus nerve within the neck.

J. D. Rolston et al.
Over the course of the 1st year, adverse events directly related to the device in the SANTE trial included paresthesias in 18.2%, implant site pain in 10.9%, implant site infections in 9.1%, and lead replacement in 8.2% of patients. Note that these frequencies include the unblinded portion of the trial—the adverse events in the blinded portion are displayed in Table 2. Adverse events that were significantly different between groups in the blinded phase were depression (14.8% of treated patients) and memory impairment (13.0%).

### Table 1: Randomized controlled trials of VNS compared with other stimulation-based therapies*

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients (no. in active group)</th>
<th>% w/ Seizure Reduction, Blinded (95% CI)</th>
<th>% w/ Seizure Reduction, 1 Yr</th>
<th>% Responder Rate, Blinded</th>
<th>% Responder Rate, 1 Yr</th>
<th>Regulatory Approval</th>
<th>FDA</th>
<th>CE Mark</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EO3</td>
<td>114 (54)</td>
<td>24.5 (14.1–34.9)</td>
<td>43</td>
<td>31</td>
<td></td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>EO5</td>
<td>196 (94)</td>
<td>27.9 (21.0–34.8)</td>
<td>45</td>
<td>23.4</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thalamic DBS—SANTE</td>
<td>109 (54)</td>
<td>40.4 (NR)</td>
<td>41</td>
<td>NR</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cortical stimulation—RNS</td>
<td>191 (97)</td>
<td>37.9 (27.7–46.7)</td>
<td>NR</td>
<td>29</td>
<td>43</td>
<td>†</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

* Seizure reduction is defined as change in actively treated patients compared with their baseline seizure frequency.Responder rates are defined as a ≥ 50% reduction in seizure frequency experienced in actively treated patients. The ≥ 50% responder rate is not reported in the SANTE trial, although it was not significantly different from the untreated group. NR = not reported.
† Pending review.
Responsive Neurostimulation

The RNS device is designed to detect seizures as they start and then stimulate the seizure focus to abort the propagation. This idea has empirical evidence supporting its feasibility.20 Responsive neurostimulation is a closed-loop system, in which subdural and depth electrodes record electrographic activity and trigger bursts of stimulation when a seizure is detected, in the hope of terminating the seizure before it is clinically apparent (Fig. 3).

In the RNS System Pivotal Trial (ClinicalTrials.gov NCT00264810), 191 patients were implanted with the NeuroPace RNS system (NeuroPace, Inc.) following a 3-month baseline period.23 Two months after surgery (and after optimizing seizure detection parameters), patients were randomized to responsive stimulation or pure detection of seizures without stimulation. Both groups were followed for 12 weeks in this blinded period (Fig. 2).

Inclusion criteria were age 18–70 years, partial seizures, medically refractory epilepsy (failure of ≥2 AEDs), 3 or more seizures per month (on average), and an EEG workup showing 1 to 2 epileptogenic regions. Over the 3-month follow-up period, stimulated patients reported a decrease in seizure frequency of 37.9%, versus 17.3% in the sham-treated group. In addition, 29% of patients reported a decrease in seizures of ≥50%, although 27% of sham-treated patients had this responder rate as well (Table 1).

As in the VNS trials and the SANTE trial, patients were followed continually after the end of the blinded phase. The RNS-treated patients continued to benefit from the device at 1 and 2 years postimplant, with 43% and 46%, respectively, achieving a ≥50% reduction in seizures (Table 1).

During the blinded evaluation period, there was no difference between the treatment and sham-treated groups in terms of reported adverse events. Nevertheless, when compiled over the study’s entire 1st year, adverse events included incision site infections in 5.2% of patients, headache in 10.5%, dysesthesia in 6.3%, increased complex partial seizures in 5.8%, increased tonic-clonic seizures in 4.7%, memory impairment in 4.2%, depression in 3.1%, and dizziness and paresthesias in 2.6%.

Adverse events that occurred strictly within the blinded phase are displayed in Table 2.

Choice of Therapy

Only VNS is approved by the FDA and therefore currently remains the primary choice of most US providers as an adjunctive treatment for refractory epilepsy (Table 1). Nevertheless, both NeuroPace and Medtronic have applied for FDA approval of the RNS System and DBS of the ANT, respectively. NeuroPace applied in July 2010 and is awaiting a panel meeting and recommendation before the FDA takes action. The FDA panel has convened and voted to approve Medtronic’s ANT DBS device. However,

**TABLE 2: Adverse events across trials***

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>VNS</th>
<th>Thalamic Stimulation (SANTE)</th>
<th>Cortical Stimulation (RNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hoarseness/voice change</td>
<td>37.2</td>
<td>66.3</td>
<td>13.0</td>
</tr>
<tr>
<td>coughing</td>
<td>7.4</td>
<td>45.3</td>
<td>12.6</td>
</tr>
<tr>
<td>nasopharyngitis</td>
<td>11.1</td>
<td>34.7</td>
<td>1.9</td>
</tr>
<tr>
<td>pain</td>
<td>5.6</td>
<td>28.4</td>
<td>3.7</td>
</tr>
<tr>
<td>dyspnea</td>
<td>5.6</td>
<td>25.3</td>
<td>9.3</td>
</tr>
<tr>
<td>headache</td>
<td>1.8</td>
<td>24.2</td>
<td>7.4</td>
</tr>
<tr>
<td>paresthesia</td>
<td>5.6</td>
<td>17.9</td>
<td>9.3</td>
</tr>
<tr>
<td>dyspepsia</td>
<td>17.9</td>
<td>9.3</td>
<td>0.5</td>
</tr>
<tr>
<td>vomiting</td>
<td>17.9</td>
<td>9.3</td>
<td>1.1</td>
</tr>
<tr>
<td>partial seizures w/ generalization†</td>
<td>14.8</td>
<td>9.3</td>
<td>4.3</td>
</tr>
<tr>
<td>complex partial seizures†</td>
<td>9.3</td>
<td>9.3</td>
<td>4.3</td>
</tr>
<tr>
<td>confusional state</td>
<td></td>
<td>7.4</td>
<td>4.3</td>
</tr>
<tr>
<td>influenza</td>
<td></td>
<td>5.6</td>
<td>2.2</td>
</tr>
<tr>
<td>simple partial seizures†</td>
<td></td>
<td>5.6</td>
<td>2.2</td>
</tr>
<tr>
<td>anticonvulsant toxicity</td>
<td></td>
<td>5.6</td>
<td>2.2</td>
</tr>
<tr>
<td>dizziness</td>
<td></td>
<td>5.6</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* All reported adverse events occurring in ≥2.5% of patients during the blinded evaluation period. — = data not provided.

† New, increased, or exacerbated.

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**Fig. 3. NeuroPace RNS Device.** This scout CT scan shows the closed-loop RNS device implanted in a patient with medically refractory epilepsy. The IPG is fixed in the skull, with penetrating depth electrodes extending into the hippocampi bilaterally. Surgical staples can also be seen surrounding the scalp flap. Image provided by Dr. Rosana Esteller, NeuroPace, and Dr. Robert Gross, Emory University.

decrease in seizure frequency of 37.9%, versus 17.3% in the sham-treated group. In addition, 29% of patients reported a decrease in seizures of ≥50%, although 27% of sham-treated patients had this responder rate as well (Table 1).

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the FDA at large rejected the panel’s recommendation, due to continued questions about the clinical data from the SANTE trial, and Medtronic continues to work with the FDA to move toward approval.

On the other hand, CE Mark approval has been granted to both VNS and Medtronic’s DBS of the ANT. Therefore, patients in Europe can take advantage of either modality, depending on patient and physician preference (Table 1).

Concerning efficacy, it is difficult to compare the trials directly, given limited access to raw data and different inclusion criteria. Both DBS of the ANT and RNS show a trend toward greater seizure reduction than VNS in blinded clinical trials (40.4% and 37.9% vs 24.5% and 27.9%, respectively; Table 1). This effect disappears in the unblinded follow-ups, however, with SANTE reporting 41%, compared with 43% and 45%, respectively, in the EO3 and EO5 trials of VNS at 1 year. Responder rates (≥ 50% reduction in seizures) show conflicting results. The VNS trials reported rates of 31% and 23.4%, both significantly different than their matched, low-stimulation groups. However, the RNS trial reported a responder rate of 29%, which was comparable to VNS but not significantly different than the RNS trial’s sham-treated group. That is, whereas patients had a significant decrease in seizure frequency compared with the control group, the number of patients experiencing a ≥ 50% reduction was not significantly different than the control group. The SANTE trial also had a response rate that was not significantly different than the control response.

Trial design is also a potential source of concern when attempting to compare the studies directly. The primary criticism for the EO3 and EO5 trials is that the “control” group was actually stimulated, just at a lower stimulation frequency. Therefore, strictly interpreted, the trials really only show significant benefit of one stimulation paradigm versus the other, as opposed to best medical management alone.

The SANTE and RNS trials avoid this pitfall by using sham stimulation with no current delivery. However, again, the significant comparison being made in these trials is DBS “on” in patients versus DBS “off” in patients. No data directly compare DBS versus best medical management. In all cases, this is because of the inherent difficulty in creating truly blinded surgical trials. The fact that the VNS trials required a device to be on, but firing at a low rate, is a testament to the high frequency of easily noted side effects by the patients, such as voice alteration and paresthesias. Patients in the SANTE and RNS trials, on the other hand, could be successfully evaluated in blinded fashion, even with the devices delivering no active stimuli.

A potential criticism of the SANTE trial is that, with intention-to-treat analysis, there was a sharp increase in the frequency of seizures in treated patients during the 1st month of blinded evaluation, with the model estimating a 19% difference between groups (that is, more seizures in the treated than control group). However, as explained in the trial’s report, this difference appears to be due to a single patient, who had 210 partial seizures in response to the on/off cycling of his DBS device during the first 3 days of stimulation. If this patient is excluded, the benefit of the DBS is more significant, but there will always be concern generated by excluding patients from final analyses. This is probably why much of the data in the SANTE trial are reported using the median, rather than the mean, because the median is less sensitive to outliers when present.

All trials restricted their analysis to patients with partial seizures and medically refractory epilepsy. Although all trials were restricted to partial seizures in patients with medically refractory disease, there are differences in inclusion criteria that might make one particular therapy more appropriate than others for particular subgroups. For example, only the VNS trials examined patients < 18
years old, so it is unclear how DBS or RNS will work in adolescent patients. However, the adolescent age group was not analyzed separately in the VNS trials, so we have no Class I evidence examining this subgroup in particular. Nevertheless, open label studies are promising, with responder rates for pediatric patients of 50% to 68%.23

An important difference between RNS and the other therapies is that all included patients in the RNS trial were required to have 1–2 identified epileptogenic foci. We do not know how the RNS system would fare in patients with nonlocalized epilepsy or in those with a larger number of foci. This particular question was addressed more directly in the SANTE trial, in which 9.3% of the stimulated patients had diffuse or multifocal epilepsy. These patients fared well, with a 35.0% reduction in seizures compared with the control group’s 14.1%, although this difference was not significant, probably due to the low number of patients within this subgroup. Neither the EO3 nor EO5 trial analyzed patients in terms of the number of epileptogenic foci, so there remains no Class I evidence for the use of VNS in this subgroup. However, unblinded trials suggest that VNS is effective in multifocal epilepsy: for example, there was a 75% seizure reduction after 3 years in one trial of adults and pediatric patients.4 Unblinded studies also support the use of VNS in epilepsy from causes such as Lennox-Gastaut syndrome, tuberous sclerosis, postinfections, and others.24 The data from the RNS system and DBS of the ANT are still developing, and as of yet the results have not addressed these alternative etiologies directly.

Adverse events appear to be most frequent with the use of VNS; for example, two-thirds of patients experience voice alteration, nearly half experience new cough, and one-quarter have headaches (Table 2). This compares with headaches in 3.7% of the SANTE patients and 2.6% of the RNS patients. Although depression and memory impairment were reported in both the SANTE and the RNS trials, they were more likely to occur with DBS of the ANT (14.8% and 13.0%, respectively) than with RNS (3.1% and 4.2%, respectively, over the entire 1st year). Moreover, these complaints were significantly more likely in actively stimulated patients in the SANTE procedure than peripheral VNS implantation. These patients fared well, with a 35.0% reduction in seizures compared with the control group’s 14.1%, although this difference was not significant, probably due to the low number of patients within this subgroup. Neither the EO3 nor EO5 trial analyzed patients in terms of the number of epileptogenic foci, so there remains no Class I evidence for the use of VNS in this subgroup. However, unblinded trials suggest that VNS is effective in multifocal epilepsy: for example, there was a 75% seizure reduction after 3 years in one trial of adults and pediatric patients.4 Unblinded studies also support the use of VNS in epilepsy from causes such as Lennox-Gastaut syndrome, tuberous sclerosis, postinfections, and others.24 The data from the RNS system and DBS of the ANT are still developing, and as of yet the results have not addressed these alternative etiologies directly.

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Some practical considerations for these devices include battery life and implications for imaging. Because DBS of the ANT requires high stimulation currents and frequent stimulation, patients require battery replacement for their device more frequently than do those being treated with VNS (yearly in some patients with DBS of the ANT vs every several years for typical VNS-treated patients). Although all devices are compatible with low-strength (1.5-T) MRI, high-field MRI is not approved while the devices are in place. Moreover, whereas VNS generators can be safely explanted, the associated stimulation cuffs cannot be, due to adherence to the nerve. There is currently no published safety information on MRI in these patients with retained stimulation cuffs. Therefore, MRIs should be performed with extreme caution in patients with explanted VNS devices, pending further study. Because DBS leads can be fully removed, this consideration is not present for DBS of the ANT or the RNS system.

**Conclusions**

There are now 3 stimulation-based neuromodulation therapies for epilepsy with positive Class I evidence: VNS, DBS of the ANT, and RNS. There are no head-to-head comparisons of these therapies, but all appear to have some limited effectiveness, and all might have application for particular subgroups of patients (Table 3). Depending on which metric is used, any one of the modalities might be viewed as more efficacious than another. The device-related morbidity appears to be specific to the surgical procedure and target of stimulation. The DBS of the ANT and RNS methods have, strictly speaking, fewer adverse events than VNS, although the makeup of events is incongruous (for example, voice changes with VNS vs depression with DBS). Moreover, the intracranial implantation of DBS leads and subdural electrodes is arguably a more invasive procedure than peripheral VNS implantation.

Importantly, however, the rate of serious adverse events such as death or paralysis was < 1%–2% across all devices. Although the RNS system has fewer reported adverse events than DBS of the ANT or VNS, the RNS system is untested on multifocal or diffuse epilepsy, whereas

**TABLE 3: Possible indications for neuromodulatory therapies***

<table>
<thead>
<tr>
<th>Indication</th>
<th>VNS</th>
<th>DBS of ANT</th>
<th>RNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adolescents (12–17 yrs)</td>
<td>likely (not specifically tested in RCTs)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>adults (&gt;18 yrs)</td>
<td>yes (Class I)</td>
<td>yes (Class I)</td>
<td>yes (Class I)</td>
</tr>
<tr>
<td>epilepsy type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>partial</td>
<td>yes (Class I)</td>
<td>yes (Class I)</td>
<td>yes (Class I)</td>
</tr>
<tr>
<td>focal (1–2 foci)</td>
<td>likely</td>
<td>likely (not specifically tested)</td>
<td>yes (Class I)</td>
</tr>
<tr>
<td>diffuse</td>
<td>likely</td>
<td>likely</td>
<td>?</td>
</tr>
<tr>
<td>generalized</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

* Question marks indicate no or inconclusive evidence. Abbreviation: RCT = randomized controlled trial.
Electrical stimulation for epilepsy

DBS seems to have benefit, although it is not statistically significant. Similarly, unblinded trials suggest that VNS is efficacious for multifocal epilepsy; however, again, Class I evidence is lacking. Adolescent patients were included in the VNS trials, whereas RNS and DBS used only patients ≥ 18 years of age, and unblinded studies support the use of VNS in pediatric patients. We will have to await further studies to determine the effectiveness of DBS of the ANT and RNS for pediatric use. Last, only VNS is FDA approved in the US, making it the only option for most patients. In Europe, both VNS and DBS of the ANT are approved, allowing more choice for patients and physicians. However, the RNS system is under review, and DBS of the ANT is also awaiting further decision on its FDA status. In the future, as more treatments become available, comparing efficacy between stimulation modalities across the broad range of causes of epilepsy will become increasingly important. However, in any case, the advent of increasingly more sophisticated methods of treating epilepsy represents great progress in the field, and the outlook for further advancements is promising.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Concept and design: Chang, Rolston. Acquisition of data: Rolston. Analysis and interpretation of data: Chang, Rolston. Drafting the article: Rolston, Englot, Wang. Critically revising the article: all authors. Reviewed submitted version of manuscript: Rolston, Englot, Wang, Shih. Statistical analysis: Rolston. Administrative/technical/material support: Chang.

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References


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