Approximately one-third of individuals continue to have seizures despite the wide range of antiseizure medications (ASMs) currently available. Resective surgery remains an efficacious form of treatment for some who have drug-resistant epilepsy (DRE). Not all DRE, however, is suitable for surgical treatment for a variety of reasons including ictal onset zones in eloquent cortex, multiple independent ictal onset zones, or poorly localized ictal onset zone(s). Patient preference may also preclude resective treatment. Although these factors pose a significant treatment challenge, nonpharmacologic neurostimulation treatment options have been approved, beginning with the first implantation of a vagal nerve stimulator (VNS) in a human in 1988. Today, nonpharmacologic, nonresective options include VNS, responsive neurostimulation (RNS), and deep brain stimulation (DBS). Having options for neurostimulation means patients and physicians have important decisions to make together. In this review, we provide an overview of each of these devices to help aid the clinician in identifying the best option to recommend for an individual patient.

**VNS**

The VNS was the first implantable neurostimulation device approved for focal DRE (in Europe in 1994 and the US in 1997). An indication for treatment-resistant depression was also approved in the US in 2007.

**Efficacy**

Primary efficacy data from 2 randomized, controlled trials led to the approval of VNS. These were the E03 (international, n=114)\(^5\)\(^-\)\(^8\) and E05 (US only, n=196)\(^9\) studies. In both trials, participants were randomly assigned to receive either high-level stimulation (active) or low-level stimulation (control) for a 14-week blinded evaluation phase. In the E03 trial, the mean seizure reduction was 25.4% among the active group and 6.1% among the control group. Responder rates (ie, proportion who had ≥50% reduction in seizure frequency from baseline) were 31% with active stimulation vs 13% with control. In the E05 trial, the mean seizure reduction was 28% among the active group vs 15% among the control group, with responder rates of 22% and 16%, respectively (not significantly different). Improved seizure control with long-term use has since been supported by subsequent studies, including in a cohort of 436 participants in whom a mean seizure frequency reduction of 55.8% and responder rate of 63.75% occurred.\(^10\) It should be noted that another potential therapeutic benefit of VNS is its efficacy in treatment-resistant depression,\(^11\) a common comorbidity of DRE.

**Adverse Effects**

VNS is generally well tolerated. Fluid accumulation at the implant site with or without infection has been reported in 1% to 2% of patients. Other side effects associated with VNS include vocal changes, throat paresthesia or discomfort, cough, and dyspnea.\(^8\)\(^-\)\(^10\) These side effects often diminish over time with continued use of the device or with adjustment of stimulation parameters (eg, current, pulse width, and frequency). In the long-term study, however, some participants with hoarseness (2.3%) or dysphagia (0.5%) did not see improvement and required removal or revision of the device.\(^10\)

**DBS**

DBS was approved for the treatment of tremor in Parkinson disease and essential tremor in the US in 1997.

Efficacy
For treatment of focal DRE, DBS stimulation is targeted to the anterior thalamic nucleus. In a randomized, double-blind controlled trial, 157 participants enrolled and 110 had DBS implanted.13 Half had stimulation turned on during a blinded phase, after which all had stimulation activated. After the blinded phase, the mean seizure frequency reduction was 40.4% in those who had stimulation vs 14.5% in those who did not. Individuals with temporal lobe seizures who had active stimulation had a significant reduction in seizure frequency (44.2%) compared with the control group (21.8%). Reductions in frontal, parietal, or occipital lobe seizures did not reach statistical significance compared with control. Responder rates were not significantly different between groups after the blinded phase. Long-term follow-up at 1 and 5 years after implantation showed continued seizure reduction.13 A constant cohort of 74 participants, defined as those who maintained seizure diaries throughout the 5-year period, had responder rates of 43% at 1 year and 68% at 5 years with median 69% reduction in seizure frequency from baseline after 5 years.

Adverse Effects
The most common adverse events observed in the first 13 months were paresthesia (18.2%), implant site pain (10.9%), and implant site infection (9.1%).12 These adverse effects reduced in frequency between years 1 and 2.13 There were no clinically significant intracranial hemorrhages, although 5 intracranial hemorrhages were incidentally found on imaging. Depression and memory impairment were reported more commonly in those who had stimulation activated during the blinded period. In the long-term follow-up study, depression was reported in 37.3% of participants at some point after implantation and 11.8% (13 individuals) reported at least 1 instance of suicidal ideation. Of those who reported depression, 66% had a history of depression prior to the device implantation. Memory impairment was reported by 27.3% of participants at some point after implantation, and approximately one-third of these individuals had formal neuropsychologic assessments that confirmed memory impairment. Approximately half of those who reported postimplantation memory concerns also had memory impairment before implantation.

RNS
The RNS system was approved in Europe and by the Food and Drug Administration (FDA) for the treatment of focal DRE with 1 or 2 foci in 2013.

Efficacy
Efficacy of the RNS device was initially reported in a double-blind, randomized trial with 240 participants, 191 of whom had device implantation.14 As in the trial of DBS, the initial 3 months of the trial were a blinded phase with stimulation and nonstimulation arms, which was followed by an unblinded phase. Mean seizure frequency reduction during the blinded phase was 37.9% for the treatment arm, compared with 17.9% for the control arm. Responder rates during the blinded phase were not significantly different. During a long-term, open-label follow-up period, seizure frequency reductions increased with time. At 1 year, mean seizure frequency reduction was 44% (n=182), which increased to 53% at 2 years (n=175), 60% at 3 years (n=214), and 66% at 6 years (n=115).15,16 Responder rates were 58% at 3 years and 59% at 6 years after device implantation.

Adverse Effects
Through the first year, 4.7% (9/191) of patients experienced an intracranial hemorrhage and 5.2% (10/191) had infections involving either the implant or incision site.14 Of the hemorrhagic complications observed, 3 were subdural hematomas caused by seizure-related head trauma and none resulted in permanent deficits. For infectious complications, all involved soft tissue only. After 2 years, there were no declines in neuropsychologic parameters; in fact, significant improvements in aspects of verbal functioning, visuospatial ability, and memory were noted.14-16 No differences in the incidence of mood-related side effects were observed in the treatment vs control group.

Clinical Decision-Making
The short answer to the question of how to choose among VNS, DBS, and RNS is that there is no short (or simple) answer. All have demonstrated safety and efficacy in people with focal DRE. There are distinctions, however, between the 3 modalities that, when recognized, may aid the clinician in determining the most appropriate choice for an individual.

All 3 devices are approved for treatment of focal DRE and are not approved to treat generalized epilepsy, although there are data supporting a potential role for VNS in generalized epilepsy.17 Long-term outcome data demonstrate continued benefit (even suggesting increasing benefit) with long-term use for all 3 devices. The Figure outlines a decision tree for a patient with DRE and how these 3 devices fit into the overall treatment of patients.

Implantation Characteristics
For some individuals, the degree of invasiveness of the procedure may be an important consideration. The VNS would be considered least invasive and does not require insertion of any
device or electrodes inside the skull. In contrast, DBS requires insertion of the stimulation electrodes intracranially. RNS requires placement of 1 or more intracranial electrodes (subdural strips on the brain surface or depth electrodes inserted into the brain) and placement of the device in the skull. For VNS and DBS, the device is typically placed in the chest.

Another distinction among devices is how candidacy for implantation is determined. VNS and DBS do not require precise localization of the ictal onset zone (only a diagnosis of focal DRE), whereas RNS is predicated on placing the stimulating electrodes on, or surrounding, the ictal onset zone. In most cases, this requires intracranial EEG to localize the area or areas (≤2) where seizures start to guide the electrode placement.

Tolerability for all 3 devices is generally good; all carry some operative risk. The specific risks of the surgeries depend, in part, on the invasiveness considerations above. Compared with VNS and RNS, higher incidences of depression have been reported with DBS stimulation of the thalamic anterior nucleus.

Programming

Although a detailed discussion of device programming is outside the scope of this review, it is worth recognizing programming differences used to adjust the stimulation or treatment across the devices. Practically speaking, programming is akin to adjusting a dose or switching between standard and long-acting formulations of medications for tolerability. VNS has a single stimulation site at the vagus nerve, whereas DBS and RNS have more than 1 implanted electrode that can be programmed. VNS and DBS cycle on and off in a regular pattern; in contrast, RNS has more than 1 therapy or stimulus paradigm so the device can deliver more than 1 form (strength or duration for example) of stimulation to disrupt seizures.

Another aspect of programming for the VNS and RNS is seizure detection. Some VNS device models have parameters to detect seizure-related changes in heart rate that can trigger stimulation. \(^9\) RNS delivers treatment in response to a detected seizure based on the intracranial EEG recorded by the device. Numerous parameters allow tailoring of detection to an individual’s seizure(s). In addition, the RNS device stores epochs of intracranial EEG that allow the physician to review and characterize reported events and tailor treatment.

Summary

There are no head-to-head comparisons of neurostimulation devices to treat focal epilepsy, so determining which is most effective is not possible. Considering efficacy is largely similar, the choice can be guided by the invasiveness, nature of seizures (eg, if more than 2 foci, RNS is not appropriate), potential adverse effects, and most importantly, patient preference. All 3 devices are important adjuncts to antiseizure medications and present a novel nonpharmacologic treatment option for those in whom resective surgery was either not fully effective or is not possible.

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