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Epilepsy (E Waterhouse, Section Editor)

Neurostimulation Devices Used in Treatment of Epilepsy

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Opinion statement

Epilepsy is a chronic neurological disorder frequently requiring lifelong treatment. In 70% of epilepsy patients, seizures are well controlled by antiepileptic medications. About 30% of epilepsy patients remain refractory to medical treatments and may need surgical interventions for better seizure control. Unfortunately and not infrequently, surgical intervention is not feasible due to various reasons such as multiple seizure foci, not resectable focus because of eloquent cortex location, or inability to tolerate surgery due to ongoing concomitant medical conditions. Neurostimulation devices have provided possible seizure control for refractory epilepsy patients who are not candidates for surgical intervention. Among them, vagal nerve stimulation (VNS) has been the oldest, in use since 1997. VNS was followed by responsive nerve stimulation (RNS) after obtaining FDA approval in 2013. Deep brain stimulation (DBS) has not yet met approval in the USA, but has been in clinical practice in Europe since 2010. Neurostimulation devices vary in how they are inserted and their mechanisms of action. VNS has been easily accepted by patients since it is placed extracranially. By contrast, DBS and RNS require invasive procedures for intracranial implantation. As use of these devices will continue to increase in the foreseeable future, we aimed to contribute to the foundation for new research to expand on current knowledge and practice by reviewing the current status of the literature.

Introduction

Epilepsy is one of the most common neurological disorders with a prevalence of 0.71% affecting over 2.2 million people in the USA [1•]. While two thirds of patients with epilepsy are controlled, one third have medically refractory epilepsy. Medically refractory epilepsy is defined as failure of seizure control despite adequate trials with at least two first-line antiepileptic medications (AEDs). In these patients, adding more medications is not likely to provide seizure control [2].

Patients with medically refractory epilepsy have a significantly increased risk of sudden unexplained

death in epilepsy (SUDEP) in addition to the burden of the disease itself, polypharmacy, and complications of seizures such as falls and trauma [3]. Hence, seizure control is very important in establishing quality of health in addition to limiting complications of the disease and its treatment. In patients with medically refractory partial epilepsy, the best chance of freedom from seizures is to remove epileptic focus by surgery. About 60% of patients with temporal lobe epilepsy, who underwent temporal lobectomy in a randomized controlled trial, were seizure-free 1 year after surgery [4•] while newer studies show that over 70% of patients remain seizure-free in the second year after temporal lobectomy [5]. However, only a group of patients with medically refractory epilepsy meet the criteria for resective surgery. This is due to the fact that in some cases, the seizure focus cannot be identified, they have multifocal epilepsy, or the seizure focus lies within the eloquent cortex. Therefore, the need for other treatment options such as neurostimulation becomes paramount in providing alternatives for better seizure control.

Neurostimulation is a treatment option for patients who are not eligible for resective surgery or who have persistent medically intractable refractory seizures despite previous epilepsy surgery. Patients with refractory epilepsy should undergo extensive investigations, including video electroencephalography (EEG), advanced neuroimaging, and even intracranial subdural or depth electrodes to decide whether seizure foci are multiple or seizure focus is in nonresectable eloquent cortex before the decision for neurostimulation is made.

At present, the primary neuromodulation modalities in use for the treatment of patients with medically refractory epilepsy are anterior nucleus deep brain stimulation (AN-DBS), vagal nerve stimulation (VNS), and responsive neurostimulation (RNS). Although unlikely to provide seizure freedom, the aim of neuromodulation treatment modalities is to reduce seizure frequency or prevent secondary generalization to minimize many risks associated with intractable epilepsy.

The potential benefits of neurostimulation, regardless of the treatment modality, are several. The mechanisms of action of neurostimulation are probably distinct from those of AEDs. Neurostimulation does not have CNS or the systemic side effects that AEDs have. While it has not yet been formally assessed, it is reasonable to predict that there is unlikely teratogenicity associated with neurostimulation.

History of neurostimulation

Neuromodulation devices were developed based on historical observations showing that stimulation of subcortical structures can modulate cortical excitability. Increased cortical synchrony mediated by low-frequency stimulation was demonstrated to be pro-epileptic, while cortical desynchronization mediated by high-frequency stimulation was shown to be antiepileptic. Initial trials of stimulation of the cerebellum and the median thalamic nucleus were unsuccessful. While unblinded studies performed were promising [6], subsequent controlled trials failed to demonstrate significant efficacy [7].

VNS was the first to be approved by the FDA in 1997. In November 2013, the neurostimulation device Neuropace, RNS, was the second to receive FDA approval.

Types of neurostimulation devices

Based on the location of the stimulation target (intracranial or extracranial) and on the method of stimulation (chronic programmed; open loop or responsive, closed loop), neurostimulation can be classified in two different ways.

The Neuropace ® RNS system and Medtronic® deep brain stimulation of the anterior nucleus of the thalamus stimulate their target directly on the cortex (intracranial). In contrast, VNS stimulates the cranial nerve in the brainstem nuclei and therefore affects the excitability of the cortex diffusely and indirectly (extracranial).

Open-loop systems provide electrical stimulation to target tissues on a preprogrammed schedule. Examples of open-loop systems are DBS and VNS systems. On the other hand, closed-loop systems detect seizure activity and provide electrical stimulation in response to an electrographic signal from the focus. The RNS system is the first closed-loop system available.

Vagal nerve stimulator

Left VNS was the first neurostimulator approved by the US Food and Drug Administration (FDA) in 1997 for the treatment of medically refractory partial-onset seizures. Approved in June 2015, the latest model of VNS, the AspireSR model, has cardiac detection mode which provides electrical stimulation in response to tachycardia, presumed to be a proxy for seizure activity. VNS requires subcutaneous implantation of the generator in the left sub-clavicular region with an electrode around the left vagus nerve.

Initial studies done in cats showed increased desynchronization of EEGs and decreased kindling of the amygdala [8]. Clinical studies involving PET showed decreased bilateral blood flow to the thalamus [9]. The exact mechanism of VNS is not well known, although its effect on cortical excitability was blocked by antimuscarinic agents and correlated with levels of norepinephrine in limbic seizure models in animals [10, 11].

The approval of VNS was based on results of two randomized controlled trials, EO3 and EO5 in 114 and 190 patients respectively [12••, 13••]. The two randomized groups were low- and high-stimulation groups. The low-stimulation group received an output current of 3.5 mA, 1 Hz, 130 μs pulse width with 30 s "on" time and 180 min "off" time. The high-stimulation group had similar output current settings but with 30 Hz, 500 μs pulse width, 30 s "on" time and 5 min "off" time. In contrast to intracranial stimulation, VNS output currents are felt by the patients; therefore, a true placebo group was not possible.

Stimulation parameters were adjusted in 2 weeks. The assessment period lasted 12 weeks. The primary outcome measure was a decrease in seizure frequency. In the EO3 study, the mean seizure reduction was 24.5 versus 6.1% in high- and low-stimulation groups, respectively, ($p = 0.01$) [12••]. In the EO5 study, the mean seizure reduction was 27.9 versus 15.2% in high- and low-stimulation groups, respectively, ($p = 0.04$). Mean seizure reduction was 55.8% at 5 years post-study. The responder rate at 1 year was 44.4% and 64.4% at 5 years [13••].

The most common side effects of hoarseness and cough are observed to reduce with time, particularly after the first year. Hoarseness occurred in up to 66% of participants and coughing was reported in up to 45% of patients in early studies [8] but this is often reduced with habituation or adjustment in stimulation parameters. After 2 years of stimulation, hoarseness was reported in

19.8%, and headache in 4.5% of patients. Serious adverse events are vocal cord paralysis (1%) and infection (1.5%) [14–16].

Anterior nucleus deep brain stimulation

The anterior nucleus of the thalamus is a core component of the Papez circuit. It serves as a relay station for outflow from the amygdala and hippocampus, fornix, and mammillary body projecting to the cingulate gyrus. The anterior thalamus has been demonstrated to be involved in seizure propagation, both experimentally and clinically, and stimulation or lesioning of the anterior nucleus (AN) pathways has been shown experimentally to have antiepileptic properties [17–19]. Therefore, inhibition of the anterior thalamus by electrical stimulation can abort seizures. This feature makes AN an important target to modulate seizure effects.

Cooper and Upton were the first to report on anterior nucleus deep brain stimulation (AN-DBS) for the treatment of refractory complex partial seizures. It was followed by a small case study series over many years [17–19]. Involvement of AN in the initiation and propagation of generalized seizures was shown in combined EEG and functional neuroimaging studies. Lesioning or high-frequency stimulation of AN increased seizure threshold and reduced epileptic activities in animal models [20, 21].

Many years later, the Stimulation of Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial was conducted to assess AN-DBS in treatment of patients with refractory epilepsy [22••].

The SANTE trial involved 110 patients who received bilateral AN electrodes. The patients were randomly assigned to stimulation ON and OFF groups. The seizure reduction rate was 40 versus 15% in the ON group and OFF group, respectively. Median seizure reduction of 41% was observed at 1 year and 69% at 5 years after implantation. Responder rate at 1 year was 43% and 68% at 5 years.

The most common reported side effect was memory loss due to possible alteration in the Papez circuit. Other reported adverse events were vocal cord paralysis and local infection.

DBS involves subcutaneous implantation of the generator in the left subclavicular region with bilateral depth electrodes in the anterior nucleus of the thalamus. It has been approved in Europe, Canada, and other parts of the world but not in the USA of yet.

Responsive neurostimulation

The first studies by Penfield and Jasper in the 1950s showed that direct cortical stimulation can suppress epileptiform discharges in humans [23]. Various modes of stimulation at different scheduled parameters targeted different anatomic regions of the brain in different studies. Initial studies stimulated the cerebellum and were followed by studies of other regions such as the hippocampus, anterior thalamic nucleus, and cortex [24–29].

As a result of these studies, an implantable, programmable system, RNS (Responsive Neurostimulator System; Neuro Pace, Mountain View, CA, USA), was designed. RNS is a closed-loop system with software designed to detect spontaneous seizures and with the ability to respond automatically with electrical stimulation. The device is implanted in the skull and is connected to one

or two intracranial depth or strip electrodes, each with one to four contacts.

The neurostimulator senses and records brain activity through depth and/or subdural cortical strip leads that are placed at that patient's seizure focus. Seizure detection is achieved by three configurable detection algorithms that are tailored to the patient's individual ictal electrographic patterns identified by the physician as abnormal. The stimulation is also adjustable in terms of frequency and amplitude. It provides brief pulses of electrical stimulation through the leads to interrupt those patterns.

A large multicenter trial using the Responsive Neurostimulation System was performed in 2011 [30••]. A total of 191 patients with medically intractable partial epilepsy were implanted with the device. The patients were randomized with either 1:1 to stimulation (treatment) or no-stimulation (sham) groups, 1 month after implantation. The first 12 weeks after randomization were blinded when safety and efficacy were assessed. The following 84-weeks of the study were an open-label period during which all patients received stimulation. Mean seizure reduction was 37.9 versus 17.3% in the treatment and the sham groups respectively (P.001). During a subsequent open-label period where all subjects received responsive stimulation, the improvement in the treatment group continued, and the sham group exhibited a decrease in seizure frequency similar to that seen in the treatment group.

Mean seizure reduction rate in seizure frequencies was 41.5% in the treatment group versus 9.4% in the sham group (P.008) at 3 months. The therapeutic effect was sustained with seizure reduction rates at 50 and 53% at 1 and 2 years respectively. The percent of patients achieving a greater than or equal to 50% reduction in seizure frequency was 44% at 1 year and 55% at 2 years.

There was no difference between the groups in reported adverse events. Adverse events during the first year included implant site pain (15.7%), headache (10.5%), and dysesthesias (6.3%) and were considered comparable with those seen with similar procedures [31]. The most common complication was intracranial hemorrhage and implant/incision site infection with a rate of 4.7 and 5.25% respectively. Infection of the brain or skull was not reported [31].

Responsive cortical stimulation using the RNS system has recently been approved by the FDA for use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with refractory partial-onset

Table 1. Differences among three neurostimulation

	VNS	RNS	DBS
Mode of action	Open loop Preprogrammed Extracranial	Closed loop Responsive stimulation Intracranial	Open loop Preprogrammed Intracranial
Side effects	Local infection Hoarseness Vocal cord paralysis	Infection Intracranial hemorrhage	Infection Intracranial hemorrhage
Long term efficacy	Seizure reduction at 1 year 26.21% and at 5 years 55.8%	Seizure reduction at 1 year 44% and at 2 years 53%	Seizure reduction from baseline at 1 year 41% and at 5 years 69%
Responder rate	At 1 year 44.5% At 5 years 64.4%	At 1 year 44% At 2 years 55%	At 1 year 43% At 5 years 68%

seizures localized to one or two epileptogenic foci. The RNS system is the first commercially available closed-loop neurostimulation system designed to treat partial-onset seizures.

Comparison of neurostimulation devices

While choosing types of neurostimulation, it is important to know the differences among them. In the decision of which type to use, many factors should be considered. Most of the important decision making factors include types of procedure, how invasive it is, costs, tolerability, and, of course, efficacy to control seizures. Although VNS is commonly chosen as the next step in refractory epilepsy patients who are not candidates for resective surgery, this practice may change while through the increased use of new neuromodulation devices, getting more comfortable with them, and gaining experience. Table 1 summarizes the differences among three neurostimulation devices in terms of side effects, tolerability, and mode of action.

Conclusions

Neurostimulation should be considered a treatment option for patients with refractory epilepsy. Although DBS and RNS are similar in terms of efficacy and safety, RNS implantation requires very precise localization of seizure foci and candidates may require intracranial electrodes for better localization of seizure foci before implantation. Patients with seizure foci on eloquent cortex or multiple independent foci would be considered potential candidates.

Compliance with Ethical Standards

Conflict of Interest
The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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