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Epilepsy (E Waterhouse, Section Editor)

Neuromodulation in the Treatment of Epilepsy

George Nune, MD[1,*]
Christopher DeGiorgio, MD, FAAN[2]
Christianne Heck, MD, MMM[1]

Address
[*,1]Department of Neurology, University of Southern California, 1520 San Pablo St. Suite 3000, Los Angeles, CA, 90033, USA
Email: george.nune@med.usc.edu
[2]Department of Neurology, University of California Los Angeles, Box 951769, 2-133 RNRC, Los Angeles, CA, 90095, USA
Email: CDegiorgio@dhs.lacounty.gov
Email: Christi.heck@med.usc.edu

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Opinion statement

Neuromodulation devices are used in the treatment of medically refractory epilepsy. This has been defined as epilepsy with persistent seizures despite adequate trials of at least two anti-epileptic drugs (AEDs). In most cases of medically refractory partial epilepsy, the first choice of treatment is resective surgery if the seizure focus can be definitively localized and if surgery can be safely performed without causing intolerable neurologic deficits. Patients with medically refractory epilepsy who are not candidates for potentially curative surgery may benefit from the implantation of a neuromodulation device. While most of these devices require surgical implantation, they provide a significant added seizure reduction without typical medication side effects. Furthermore, the efficacy of these devices continues to improve over years. There are currently no head-to-head trials comparing the different neuromodulation devices but efficacy appears to be roughly similar. The choice of device therefore depends on the type of epilepsy, whether the seizure focus can be identified, and other clinical factors. Vagal Nerve Stimulation (VNS) does not require identification of the seizure focus and also carries an FDA indication for depression. While in the United States VNS is only approved for use in partial epilepsy, it is commonly used off-label to treat generalized seizures as well. VNS delivers stimulation on a scheduled basis, in response to patient activation, or in response to heart rate increases serving as a proxy for seizures. Responsive Neurostimulation (RNS) requires the identification of up to two seizure foci and delivers stimulation only in response to the detection of epileptiform activity. While it requires intracranial placement of electrodes, it allows for long-term monitoring of electrographic seizures and may be effective where VNS has not

produced an optimal response. Deep brain stimulation of the anterior nucleus of the thalamus is not FDA approved at this time but is available in Europe and many other parts of the world. While it also carries an indication only for partial epilepsy, it does not require identification of the seizure focus and may be particularly helpful for temporal lobe epilepsy. It also appears effective in cases where VNS has not been sufficiently helpful. The Trigeminal Nerve Stimulation (TNS) system is another treatment modality which is not yet FDA approved but is available in Europe and other countries. Its mechanism of action is similar to the VNS system and it also appears to have anti-depression effects in addition to anti-epileptic benefits. However, the most compelling feature of TNS is that it is not implanted but rather applied to the skin with transdermal electrodes, typically at night.

Introduction

Epilepsy is a common neurologic disorder with the prevalence in the USA estimated at 0.71 % of the population or over 2.2 million people [1]. Of these patients, approximately one third are considered medically refractory, meaning that they continue to suffer from seizures despite adequate trials of at least two first-line anti-epileptic medications (AEDs) [2]. In these patients, adding more medications is not likely to render them seizure free. Not only is the quality of life severely impacted in patients with medically refractory epilepsy but they are also at a significantly increased risk of sudden unexplained death in epilepsy (SUDEP) [3]. Many patients are therefore willing to undergo invasive procedures and novel therapies with the hope of decreasing disease severity.

In patients with medically refractory partial epilepsy, the best chance of seizure freedom is surgery to resect the epileptic focus. For example, in temporal lobe epilepsy nearly 60 % of patients who underwent temporal lobectomy in a randomized control trial were seizure-free at 1 year after surgery [4] while newer studies show that over 70 % of patients are seizure-free in the second year after temporal lobectomy [5•]. However, only a subset of patients with medically refractory epilepsy are candidates for resective surgery. This may be due to the fact that the seizure focus cannot be identified, they have multifocal epilepsy, or the seizure focus lies within eloquent cortex.

Neuromodulation devices use electrical stimulation to decrease the excitability of the brain and thereby decrease the frequency or duration of seizures. Of the best established therapies, the Neuropace ® RNS system and Medtronic ® deep brain stimulation of the anterior nucleus of the thalamus act directly on the brain. In contrast, Vagal Nerve Stimulation (VNS) and Trigeminal Nerve Stimulation (TNS) act on cranial nerves with stimulation ascending through brainstem nuclei and affecting the excitability of the cortex diffusely. Another important distinction among neuromodulation devices is between open-loop and closed-loop systems. Deep-brain stimulation for epilepsy, TNS, and the traditional VNS system are open-loop systems, which simply provide electrical stimulation to target tissues on a pre-programmed schedule. In contrast, closed-loop systems detect seizure activity and provide electrical stimulation in response. The RNS system was the first closed-loop system available. It detects electrographic seizure activity by monitoring the electrocorticographic signal and immediately provides stimulation to the seizure focus. Additionally, the latest model of the VNS, the AspireSR model, has an optional cardiac detection mode which provides electrical stimulation in response to tachycardia presumed to be a proxy for seizure activity.

Neuromodulation devices have several benefits over surgery as well as medications. First, they lack typical systemic or neurologic medication side effects. Intracranial stimulation is not typically felt. While VNS may trigger cough, voice changes, or parasthesias, these are dose-dependent and can usually be minimized by decreasing the intensity of therapy. TNS also appears to have very mild stimulation-related side effects. With the exception of TNS, these devices are surgically implanted and therefore carry the risk of infection or other surgical complications. They also require minor surgeries to replace the generator with battery depletion every 2–10 years. However, compared to resective surgery, neuromodulation devices are considerably less invasive and are reversible in that they can be removed. One of the main benefits of neuromodulation devices is that with use, efficacy improves over time. The initial Phase III randomized control studies of these devices showed an improvement in seizure frequency comparable to the addition of a new medication in patients with medically refractory epilepsy [6–8] but long-term follow-up studies covering several

years show that efficacy improves to over 60 % median seizure reduction from baseline [9••, 10••, 11]. This is theorized to be due to long-term changes in the excitability of epileptogenic networks. Quality of life has also been shown to improve significantly with neuromodulation [12•].

The choice of device in the treatment of medically refractory epilepsy is based on a number of factors but it is not clear whether one device is more efficacious than the others. Long-term data for several years of follow-up suggests that VNS, RNS, and stimulation of the anterior nucleus of the thalamus have similar efficacy but TNS is pending a larger Phase III trial. Only VNS and RNS are FDA approved and are therefore the only devices available in the USA but TNS and stimulation of the anterior nucleus of the thalamus are available in Europe and other countries. While all the devices discussed are approved for partial onset epilepsy, only RNS requires clear identification of the seizure focus. Stimulation of the anterior nucleus of the thalamus may be particularly useful for temporal lobe epilepsy. VNS and TNS may be helpful for generalized seizures as well as depression. Due to its less invasive nature, some patients may find VNS preferable to the intracranial devices while TNS does not require implantation at all, exposing patients to minimal risk. Both RNS and stimulation of the anterior nucleus of the thalamus appear to be effective in patients who have not adequately responded to VNS or past surgery. Lastly, RNS may provide long-term ECoG monitoring, which may be useful in certain cases.

Treatment

Neuromodulation devices

Vagal nerve stimulation

Indications	Medically refractory partial onset seizures or major depression. Commonly used for generalized seizures as well [13••].
Availability	FDA Approved since 1997. Model with tachycardia detection approved June 2015.
Implantation	Subcutaneous implantation of the generator in the left sub-clavicular region with electrode around left vagus nerve.
Open/Closed Loop	Open loop except for new AspireSR (Model 106), which delivers stimulation based on increases in heart rate of at least 20 %. The patient may activate on-demand stimulation in all models by swiping a magnet over the device.
Stimulation Parameters	Begin at a current of 0.25 mA, frequency 20–30 Hz, pulse width 250–500 μs, 30 s ON, and 5 min OFF. Gradually increase current intensity as tolerated in 0.25 mA increments up to 1 to 1.5 mA or more. If side effects become limiting, reduction in pulse width to 250 μs or in frequency to 20 Hz may improve tolerability. If patients fail to respond, one may increase the duty cycle by incrementally reducing the OFF time. The duty cycle should not exceed 50 % [14].
Efficacy	The largest long-term study documented a median seizure reduction of 35 % at 1 year and 44 % at 3 years [15]. A smaller long-term study documented a 65.7 % seizure reduction at 6 years after implantation and a 75.7 % seizure reduction at 10 years [16].
Common Adverse Events	Hoarseness occurred in up to 66 % and cough in up to 45 % of patients in early studies [8] but this is often reduced with habituation or adjustment in stimulation parameters. By 2 years of stimulation, hoarseness was reported in 19.8 % and headache in 4.5 % of patients [15].
Severe Adverse Events	Vocal cord paralysis 1 %, infection 1.5 % [8]

Responsive neurostimulation system

Indications	Medically refractory partial onset seizures with up to two identified seizure foci.
Availability	FDA approved since 2013.
Implantation	Stimulator implanted within the skull and connected to any combination of up to two depth or subdural strip electrodes implanted in or over the seizure foci.
Open/Closed Loop	Closed loop. Physician identifies epileptiform discharges to be treated. The device stores electrocorticograms (ECoGs) of epileptiform or electrographic seizure activity and logs temporal patterns of detection events.
Stimulation Parameters	Therapy consists of up to five sequential stimulations in rapid succession, each of which is made up of two bursts. Typical starting stimulation parameters are current of 1 mA, pulse width 160 μs, frequency 200 Hz, and burst duration 100 ms. The stimulation path can be configured by setting the polarity of individual electrode contacts. For example, it is recommended that bipolar stimulation be used for temporal lobe epilepsy with adjacent positive and negative contacts (+−+−and+−+−) while in neocortical epilepsy each electrode may have all the contacts set to a single polarity so as to stimulate a larger stimulation area between subdural strips (++++ and −−−−). The charge density is gradually adjusted up to 3μC/cm^2 after which frequency may be adjusted gradually.
Efficacy	Median percent seizure reduction from baseline is 44 % at 1 year and 65.7 % by year six after implantation [9••].
Common Adverse Events	Stimulation is unlikely to cause appreciable symptoms.
Serious Adverse Events	Implant site infection 9.4 %, hemorrhage 4.7 % [9••]

Deep brain stimulation of the anterior nucleus of the thalamus

Indications	Medically refractory partial onset seizures.
Status	Approved in Europe, Canada, and other parts of the world but not in the USA.
Implantation	Subcutaneous implantation of the generator in the left sub-clavicular region with bilateral depth electrodes in the anterior nucleus of the thalamus.
Open/Closed Loop	Open loop.
Stimulation Parameters	Starting stimulation parameters typically current of 5 V, frequency 145 Hz, pulse width 90 μs, 1 min ON, and 5 min OFF.
Efficacy	Median seizure reduction of 41 % at 1 year and 69 % at 5 years after implantation [10••]. Temporal lobe epilepsy may respond best.
Common Adverse Effects	Implant site pain 23.6 %, paresthesias 22.7 % [10••]
Serious Adverse Events	Implant site infection 10 %, leads not within target 8.2 % [10••]

Trigeminal nerve stimulation

Indications	Medically refractory partial onset seizures and depression. As with VNS, it may be helpful for generalized seizures as well.
Status	Available in Europe and other parts of the world for treatment of depression or epilepsy. Not yet FDA approved.
Implantation	Not implanted. The device is worn externally for at least 12 h per day and uses transdermal electrodes to stimulate supraorbital branches of the trigeminal nerve.

Open/Closed Loop	Open loop
Stimulation Parameters	Frequency 120 Hz, pulse width 250 μs, up to 30 s ON, and up to 30 s OFF.
Efficacy	Decrease in seizure frequency of 27.4 % at 6 months and 34.8 % at 12 months in the active treatment group of the Phase II trial [17••].
Common Adverse Effects	Skin irritation 14 %, headache 4 %, and anxiety 4 %
Serious Adverse Events	None

Pediatric considerations

- TNS is approved for children 9 years and older in Europe.
- VNS is FDA approved for children over 12 but has been used in the wider pediatric population [13••].

Compliance with Ethics Guidelines

Conflict of Interest

George Nune reports research support without any direct financial benefits from Neuropace Inc. and Cyberonics Inc. during the conduct of the study.

Christopher DeGiorgio was previously an employee of Neurosigma Inc. and co-owns relevant patents from which he has received royalties.

Christianne Heck reports non-financial support and other research support from Neuropace Inc and other support from NeuroSigma during the conduct of the study.

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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