The anchor of epilepsy surgery is the resection of a presumed seizure focus or disruption of seizure propagation pathways. Unfortunately, these approaches cannot be applied to all patients with medically refractory epilepsy (MRE). But since 1997, vagus nerve stimulation has been a palliative adjunct to the care of MRE patients. Electrical stimulation of both central and peripheral nervous systems offers a possible alternative for patients who are deemed poor candidates for resective procedures.

About 50 percent of patients with VNS have a seizure reduction greater than 50 percent, but unfortunately, less than 10 percent become seizure-free. A recent meta-analysis of 74 clinical studies with 3,321 patients suffering from intractable epilepsy found that patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Furthermore, post-traumatic epilepsy and tuberous sclerosis were positive predictors of a favorable outcome. Patients can see an alerting effect after VNS that may allow a reduction in sedating medications. The major adverse event is hoarseness, and patients may not improve until several months after VNS implantation, but treatment is generally well tolerated.

To find out more about recent findings and where the research is heading, Practical Neurology talked to David Spencer, MD, Associate Professor of Neurology at Oregon Health and Sciences University, Associate Director of the OHSU Comprehensive Epilepsy Program, and OHSU Neurology Residency Program Director.

What type of epilepsy patient is a candidate for neurostimulation? What does the research tell us about neurostimulation in regard to reducing seizure frequency and improving quality of life?

Clinicians’ practices vary substantially in the selection of patients for VNS. Some may consider this therapy early, if the first two to three trials of medications are not working well enough, while others reserve its use only after more extensive medication trials have failed. In my own practice, I consider VNS in patients whose seizures are refractory to medication and who are not good surgical candidates. This latter criterion is important, because epilepsy surgery often has a high potential to render the patient seizure free, whereas this is not an expectation of VNS therapy. I tend to reserve VNS therapy for patients who have gone through trials of most reasonable medications for their epilepsy. This does not mean an exhaustive trial of every medication in every combination. To me, this means use of those medications that are appropriate for the epilepsy syndrome and that have a reasonable chance of working and reasonably low chance of causing side effects. Most comparisons of VNS to the newer medications show roughly similar responder rates. If a medication is not working, it can be stopped fairly easily, but VNS therapy is a longer-term commitment. I do consider VNS therapy earlier in the course of treatment for the medication sensitive patient who has experienced side effects with many/most medication trials.
The profiles of patients who could be considered for other forms of neurostimulation are not yet defined, as none of these therapies are yet approved. These therapies may initially be more limited to specific patient populations, but this will likely change and potentially expand as greater experience is gained.

**Vagus nerve stimulation is well-established as the leading neurostimulation for epilepsy. Do any new devices show potential? Are there any promising leads for different brain targets?**

There are two new devices that have completed major clinical trials of neurostimulation in epilepsy. The first involved stimulation of the anterior nucleus of the thalamus (the "SANTE" trial). This was a relatively large study involving 110 participants that showed positive effects of stimulation on seizure control. An FDA advisory panel initially recommended approval, but it ultimately did not receive full FDA approval and its fate is uncertain. A second device, the NeuroPace RNS device, takes a different approach. This therapy can target one or two seizure foci using a device that rapidly detects seizure activity in the brain and delivers responsive stimulation that attempts to terminate the seizure before it causes clinical symptoms. The pivotal trial of this device has been completed and data are before the FDA. Other trials of stimulation, including the use of transcranial magnetic stimulation—using an external device to stimulate the brain using magnetic energy—are underway. Stimulation of other cranial nerves besides the vagus nerve is being investigated.

**VNS has been FDA-approved for seizure treatment since 1997. What, if anything, has changed with VNS?**

Vagus nerve stimulation is now a well-recognized therapy for epilepsy. The approval of this device opened up new options for the treatment of difficult to control focal-onset ("localization-related") epilepsy. Since the well-controlled studies that led to the approval of the device, there have been few new rigorous scientific studies of the device. High quality scientific studies are still lacking that might support expanded use of the device in other types of epilepsy, or guide physicians in optimizing stimulation parameters. The device has undergone incremental improvements in size and battery design, but the fundamental approach has remained unchanged. More innovative enhancements to the current device have been investigated but are not currently available.

Dr. Spencer is an investigator for the NeuroPace RNS device.

**Recent Findings in VNS**

New research indicates that physicians should monitor patients’ sleeping habits before and after the VNS procedure, due to the complex relationship between epilepsy and OSA. VNS causes an increase in respiratory rate, decrease in respiratory amplitude, decrease in tidal volume, and decrease in oxygen saturation during periods of device activation. These respiratory events can be reduced with changes in the vagus nerve stimulator operational parameters or with the use of CPAP. Typically, it does not cause an arousal or a change in heart rate or blood pressure. The authors note that, “in particular, patients with refractory epilepsy need assessment for undiagnosed and untreated obstructive sleep apnea before implantation of vagus nerve stimulator devices. Patients with vagus nerve stimulators often have an increase in apneic events after implantation, and these patients need screening for sleep apnea both before and after implantation.”

In addition to well-established treatments such as vagus nerve stimulation, epilepsy centers around the world are investigating the safety and efficacy of neurostimulation at different brain targets, including the hippocampus, thalamus, and subthalamic nucleus. Also promising are preliminary results of responsive neuromodulation studies, which involve the delivery of stimulation to the brain in response to detected epileptiform or preepileptiform activity.

---Zac Haughn, Senior Associate Editor---

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