Neurostimulation for Epilepsy

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Hauser and colleagues have estimated the lifetime prevalence of epilepsy to be 1-3% of the population at large. Despite the impressive recent advances in anti-epileptic drug (AED) therapies, only ~70% of patients are seizure-free with AED therapy, alone or in combination, with 30% or more remaining medically refractory. Refractory epilepsy poses significant psychosocial, financial, and physical burdens to patients and their families and a major societal burden in loss of time from work and school. Treatment options for refractory patients include resective brain surgery, the ketogenic diet (in children), experimental therapies, and vagal nerve stimulation (VNS).

When patients with partial epilepsy are found to be medically refractory, surgical resection of the seizure focus becomes a primary option. However, not all patients are determined to be appropriate surgical candidates after pre-surgical evaluation, and a subset are reluctant to undergo brain surgery. In such patients, neurostimulation with VNS is a viable treatment option that should be considered.

History of Vagal Nerve Stimulation

Bailey and Bremer conducted pioneering studies concerning the physiologic effects of VNS in 1938. Subsequent animal studies demonstrated desynchronization of EEG activity with vagal nerve stimulation, and later demonstrated anticonvulsant properties. In 1988, the first human patient was implanted with a VNS. Subsequently, VNS has been substantially improved, extensively studied, and made routine. Pivotal multicenter studies in the 1990s led to the 1997 FDA approval of an implantable device made by Cyberonics, Inc. named the NeuroCybernetic Prosthesis (NCP) as an add-on treatment option for medically refractory partial epilepsy, in patients over 12 years of age. As of 2005, more than 25,000 patients worldwide have been implanted with the device for the treatment of epilepsy. This year, the FDA approved VNS for the treatment of medically refractory depression.

Mechanism of Action

The exact mechanism of action of VNS is unknown. VNS mainly excites afferent fibers that terminate in the nucleus of the tractus solitarius (NTS). The NTS, in turn, projects to the parabrachial nucleus, which has projections to various CNS targets that are known to play key roles in seizure onset and propagation. These include the hippocampus, amygdala, and hypothalamus. As well, the NTS has important connections to the raphe nuclei and the locus ceruleus, both utilizing noradrenergic transmission and both with extensive cortical projections. Depletion of CNS noradrenergic transmission in animal models attenuates the anticonvulsant effects of VNS. Functional brain imaging studies such as positron emission tomography (PET) scanning suggest that widespread CNS circuits are impacted by VNS.

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Clinical Trials: Efficacy

Both studies demonstrated statistically significant differences in efficacy between the high- and low-intensity treatment arms. In EO3 (114 patients) the mean reduction in seizure frequency was 24.5% for the high-intensity group vs. 6.1% for the low-intensity group. The responder rate for the high-intensity group was 31%. In EO5 (196 patients) the high-intensity arm had a mean seizure reduction of 28% vs. 15% for the low-intensity arm. Although the responder rate in EO5 was not statistically significant over the first three months of study, open label extension studies from the EO1-5 studies showed median seizure reduction rates of 44% and responder rates of 43% by two years. This observed delay in achieving the full therapeutic effect of VNS has raised the notion that there may be beneficial long-term physiological CNS changes that accrue with this therapy.

Clinical Trials: Adverse Events

VNS adverse events can be grouped into those associated with implantation and those associated with subsequent everyday use. Important peri-operative side effects include infection, bleeding, vocal cord paralysis (due to injury to the left recurrent laryngeal nerve, a branch of the vagus), lower facial paralysis, pain, cough, nausea, and voice change. Generally, peri-operative side effects resolved. Infrequently, postoperative infection required explantation.

The adverse event profile associated with everyday use was similar in the two pivotal studies. These involved hoarseness, throat pain, cough, dyspnea, paresthesia, and mild muscle pain. Such side effects appeared to be related to intensity of VNS settings (dose) and were rated as mild to moderate. Most resolved after the first year of use in open label follow-up studies.
Implantation and Programming

The NCP is comprised of a battery-powered generator with a connecting cable, terminating in helical contact electrodes. (Figure). The left vagus nerve is used for VNS to avoid cardiac dysrhythmia; fibers from the right vagal nerve innervate the sinoatrial node.

Implantation of the device is typically performed under general anesthesia and usually takes one to two hours, often as an outpatient surgery. The electrodes are gently looped around the left vagus nerve, once it is exposed via an incision along the anterior border of the sternoclavicular. The generator is placed over the left chest, inside a subcutaneous pocket made along the pectoral fascia. The mean battery life of the current model NCP generator is 8-12 years. When the battery life wanes, the generator must be surgically replaced. Finally, the generator and the electrodes are connected via a subcutaneous tunnel between the two locations, before the leads are tested with appropriate monitoring.

Many centers wait 1-2 weeks before activating the device. Programming the generator is straightforward, using a hand-held, computer-driven wand to “instruct” the generator regarding stimulation parameters. With successive visits, the device settings are gradually ramped up to target stimulation goals. Using this graduated approach, one may minimize the side effects mentioned in the prior section. Some centers later adjust the timing of the stimuli. Default settings are 30 seconds on, 300 seconds off. However, the device may be cycled more frequently and this may prove beneficial in some cases. In addition to its “round-the-clock” pattern of stimulation, the device is programmed to deliver a pre-set pulse in response to activation with a magnet provided to patients. This mode of use may help attenuate threatened seizure activity in some instances.

Role of VNS

VNS therapy has been approved for add-on use in patients with refractory partial epilepsy, in those 12 years and older. It has mainly been used when epilepsy surgery is deemed unwise or unacceptable to the patient, or when AED-related complications become untenable. It goes without saying that epilepsy surgery in well-selected patients offers the greatest chance for seizure-freedom. But there is a still sizeable fraction of refractory patients for whom surgery is unlikely to be helpful (e.g. multifocal patients, non-lesional extra-temporal patients). VNS has also been studied in other populations (though not FDA approved for such); it has been extensively used off-label in children with refractory epilepsy and in patients with refractory generalized epilepsy. It appears to be particularly valuable to patients with drop attacks, as in Lennox-Gastaut syndrome. Indeed, it has nearly replaced the corpus callosotomy for such patients, seeking respite from injurious drop attacks.

Its efficacy in pivotal studies appears to be comparable with that of many of the newer AEDs, though it has not been compared in a head-to-head fashion. For example, two newer generation AEDs, gabapentin and topiramate, demonstrated responder rates of 28.5% and 45.7%, respectively. The safety and tolerability profiles of VNS are very good and, arguably superior to many available AEDs. It poses no drug interactions, does not contribute to dizziness or lethargy (usual AED CNS side effects), and carries no compliance burden. Important shortfalls of VNS include the requirement for surgery, lack of truly curative potential, and interference with the ability to obtain neck or body MRIs after implantation (fear of thermal injury to the vagal nerve). Prior cosmetic concerns have improved with strides in design.

Experience at Rhode Island Hospital

At the Rhode Island Hospital Comprehensive Epilepsy Program, we have implanted ~120 patients over the past 5 years with the VNS. Of these VNS recipients, approximately 50% are followed in our center. Neurologists within surrounding communities are following the other recipients. In our own experience, a high percentage of patients and their families are pleased with this mode of therapy. Improvement is frequently described to us, not only in reduced seizure tallies, but in other important ways. Many patients have decreased their AEDs post-VNS, leading to reduced side effect burden and greater compliance. Other patients have commented on shorter seizures and faster recoveries with shortened post-ictal phases. Some families can use the “magnet mode” to abort a threatened seizure or a seizure cluster. Many families comment on improved alertness with VNS. There appears to be a modest but significant mood benefit as well. For all these reasons, satisfaction rates with VNS appear high. It remains to be seen what fraction of VNS patients will elect to re-implant their generator upon the battery’s end of service. We anticipate that this will be the majority of VNS recipients.

Future Directions

Deep brain stimulation has become nearly commonplace in the treatment of Parkinson’s Disease. By contrast, direct CNS stimulation is still a subject of active investigation in epilepsy. Numerous CNS structures have been studied to date. Cerebellar stimulation was initially tried in epileptic patients with mixed results. Subsequently, various cortical and subcortical loci have been pursued. Different groups are currently exploring diverse stimulation paradigms. For instance, Fisher and colleagues have been studying thalamic stimulation (anterior and centromedian nuclei). A phase II trial of anterior thalamic stimulation for refractory epilepsy is underway. This approach, in theory, is not predicated upon knowledge of the seizure focus. It relies upon the widespread connections between thalamus and cortex to exert its effects. It is therefore a non-specific approach, much like VNS.

Other groups have targeted the
actual seizure focus. Both neocortical and limbic structures have been targeted in this paradigm. This requires detailed knowledge of the focus and relies upon indwelling subdural strips or grids to deliver stimuli to target structures. An underlying hope for this line of research is to ultimately devise a “closed loop” system in which the implanted grid contacts facilitate computerized detection of nascent or threatened seizure activity. This would trigger the delivery of electrical stimuli to a subset of the grid electrodes to abort or attenuate the threatened seizure. One prototype of this approach has been dubbed the Responsive Neuro-stimulating (RNS) device. This elegant and “high-tech” approach has theoretical appeal but presumes pivotal advances in both seizure detection methodology and in neurostimulation to bring it to fruition.

Conclusion
VNS is the only FDA-approved form of neurostimulation for the treatment of epilepsy. Its specific indication is for medically refractory patients with partial epilepsy, age twelve and older. However, studies have also indicated efficacy in generalized seizure disorders and in children. Resective brain surgery still offers the greatest hope for seizure-freedom in refractory partial epilepsy but only a subset of patients are found to be good surgical candidates. For the remainder of refractory patients, VNS offers an important therapeutic alternative. It also offers the chance to reduce some of the burden of AED therapy for such patients, and appears to have salutary mood effects in some populations. It is recommended that patients with refractory epilepsy be considered for referral to comprehensive epilepsy programs to permit stratifying such patients for advanced treatment options, including VNS. Once implanted, the device is easily programmed, is generally very well tolerated by patients, and has an excellent safety profile. Finally, other forms of neurostimulation are being studied that offer great hope for future improvements in epilepsy treatment. We may look back one day and observe that VNS represents the start of an important paradigm shift in the treatment of epilepsy.

References

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