Should I offer vagus nerve stimulation as part of my neurology practice?

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Summary

Vagus nerve stimulation (VNS) is a safe and effective adjunctive therapy approved for patients with partial-onset seizures. A pulse generator, which is implanted in the chest wall, delivers programmed electrical pulses through an electrode that is attached to the left vagus nerve. VNS plays an important role in the treatment of patients with drug-resistant epilepsy. It is currently offered in academic as well as private practice settings. After a comprehensive workup is performed, VNS should be offered to patients with drug-resistant epilepsy who are not candidates for surgery.

Epilepsy affects nearly 3 million Americans of all ages and approximately 50 million people worldwide.¹ There are approximately 200,000 new cases of epilepsy diagnosed each year.² It is not surprising that the care of patients with epilepsy is an integral part of any neurology practice. While most neurologists feel fairly comfortable initiating antiepileptic drugs (AED) to their patients, we have learned over the past decade that some patients have poor response to medications for seizure control. Furthermore, as advancements are made in treatment modalities, neurologists must be aware of the options available to them and which therapies are best for particular patients.

Drug-resistant epilepsy has become an extremely important concept in the care of patients with epilepsy. A paramount study by Kwan and Brodie³ in 2000 found that 47% of newly diagnosed patients with epilepsy became seizure-free after treatment with their first AED. Of those who did not respond to the first AED, 14% became seizure-free with treatment of a second or third AED. Only 3% of patients became seizure-free while taking 2 medications. Importantly, only 11% of those who failed their first medication ever became seizure-free with medication alone. This suggests that we should be able to identify individuals with refractory epilepsy early in their treatment course. Taking these important observations into account, the International League Against Epilepsy has proposed that drug-resistant epilepsy be defined as “failure of adequate trials of 2 tolerated and appropriately chosen and used AED

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If a patient with refractory epilepsy is a good candidate for surgical resection, then this should be pursued above all other modalities.

schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”⁴ It is now evident that response to first and second antiepileptic medications not only indicates a favorable prognosis but will enable us to predict early on those patients who could possibly benefit from a different form of therapy.

When to refer?

It is imperative that patients who have met criteria for drug-resistant epilepsy receive the appropriate workup to confirm the diagnosis of epilepsy and identify an epilepsy syndrome, if possible, in order to dictate further steps in their treatment. This typically includes neuroimaging, video-EEG monitoring, and neuropsychological testing. In some cases the diagnosis of epilepsy may be in question and this workup is essential in ruling out psychogenic nonepileptic events. Occasionally patients with “drug-resistant epilepsy” in fact have nonepileptic events that are not likely to respond to any of the standard medication therapies for epilepsy.⁵

Most general neurologists do not have direct access to the services that entail a comprehensive diagnostic workup for medically refractory epilepsy. In keeping with guidelines set forth by the National Association of Epilepsy Centers (NAEC), it is recommended that general neurologists refer a patient to either a Level 3 or Level 4 specialized Epilepsy Center if they are unable to control their patient’s seizures after 12 months.⁶ A Level 3 Epilepsy Center offers the “basic range of medical, neuropsychological, and psychosocial services needed to treat patients with refractory epilepsy.”⁶ This includes noninvasive evaluation for epilepsy surgery, straightforward respective surgeries, and vagus nerve implantation. A Level 4 Epilepsy Center provides these same services as well as invasive evaluation for epilepsy surgery, which would be intracranial electrode placement, in addition to more complex resective epilepsy surgeries.⁶

Surgery vs vagus nerve stimulation

Of the one-third of patients who have drug-resistant epilepsy, and in whom nonepileptic events have been ruled out, evaluation for surgical intervention should be considered first if appropriate. Patients who are candidates have a resectable seizure focus or other resectable lesion that can be removed without causing major neurologic or cognitive dysfunction. There is evidence to suggest that surgical resection offers appropriately selected patients with drug-resistant epilepsy a greater chance at seizure freedom than medication alone. In one study in particular, 58% of patients who had temporal lobectomy became seizure-free vs only 8% with best medical therapy after 1 year.⁷ When resective surgery is not an option, consideration of other nonpharmacologic therapies is appropriate and should be considered. This includes vagus nerve stimulation (VNS) and ketogenic diet, the latter of which is not within the scope of this article.

In 1999, the American Academy of Neurology issued a position paper stating that the effectiveness of VNS is comparable to that of new AED but lower than that of mesial temporal lobectomy.⁸ Despite Class I evidence and current guidelines, epilepsy surgery is still underutilized. The number of lobectomies and partial lobectomies for drug-resistant epilepsy in the United States did not change significantly from 1990 to 2008.⁹ This is despite an estimated 100,000 to 300,000 patients with refractory epilepsy who were potential surgical candidates according to a survey done in 1990.⁹ One of the many possible explanations for this trend may be, in fact, that some patients are opting for a palliative option such as VNS. While this has proven to be safe and effective, it less often results in seizure freedom. If a patient with

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refractory epilepsy is a good candidate for surgical resection, then this should be pursued above all other modalities.

VNS efficacy data

Many patients with drug-resistant epilepsy are not good candidates for surgery due to poorly localized epilepsy or proximity of the lesion to eloquent cortex. In addition, many patients have significant comorbidities that would complicate surgery or they simply refuse it as an option. In these patients, VNS should be considered as a suitable option to potentially reduce seizure burden.

VNS was approved in 1997 by the US Food and Drug Administration as adjunctive therapy for adults and adolescents over age 12 years for drug-resistant partial-onset seizures. Five clinical trials were performed between 1988 and 1995 (E01–E05) and data were collected on a total of 440 patients. The 50% responder rate, which is the percentage of patients with a $\geq 50\%$ reduction in seizures, was 37% at 1 year, 43% at 2 years, and 43% at 3 years.¹⁰ Median seizure reduction compared to baseline was 35% at 1 year, 44% at 2 years, and 44% at 3 years.¹⁰ The efficacy of VNS tends to increase over time, plateauing between 18 and 24 months.¹⁰ A long-term outcome study showed that after 1 year, patients with VNS and unchanged AED had a median 58% improvement in seizure rates.¹¹

Typically the left vagus nerve is accessed by the surgeon (general; ear, nose, and throat; vascular; or neurosurgeon) to place the electrode while the device itself is placed in the chest wall. Efferent cardiac fibers from the right vagus nerve that innervate the sinoatrial node pose a theoretical risk of bradycardia, which makes left-sided procedures preferred. However, rare cases of cardiac side effects including bradycardia and asystole have mainly occurred intraoperatively during lead tests using high current.^{12–14} VNS is well-tolerated with the most common side effects being hoarseness (28%) and paresthesias (12%) after 1 year. These side effects have been shown to become more tolerable or diminish over time.¹⁵

VNS training

The idea of programming a VNS device may be intimidating to some practitioners but the truth is that managing patients with VNS can be relatively simple. Familiarity with only a few programmable parameters including output current, frequency, pulse width, and ON/OFF times is needed. Settings are manipulated with the goal of maximizing efficacy as well as patient tolerability. One must also keep in mind that certain settings can have a greater effect on battery life.

Output current, which is the amplitude of the current delivered in a single pulse of stimulation, is measured in mA and ranges from 0 (off) to 3.5 mA. Typically the output current is set at 0.25 mA either immediately after surgery or after a 2-week recovery period. It can then be increased in 0.25–0.5 mA intervals every 2–4 weeks as tolerability allows. Titration continues, which allows patients to develop tolerance over time. Typical output currents range from 1.0 to 2.0 mA. Side effects pertaining to increases of output current include hoarseness or voice alteration, cough, sensation of throat tightening, and dyspnea.¹⁶ Patient tolerability to these side effects usually improves over time. Once a patient can tolerate an output current of 1.0 mA, a lead test (system diagnostics) can be performed. Exposure of 1.0 mA of current to a naive nerve can be uncomfortable and incurs a potential risk of asystole.¹⁶

Frequency refers to the repetition rate of the individual pulses and is measured in the number of pulses per second (Hz). Frequency ranges from 1 to 30 Hz. Clinical studies have shown that VNS should be set at an initial frequency of 30 Hz for patients with epilepsy.¹⁷ The frequency should not be set at 5 Hz or lower as this has been shown to decrease effectiveness and depletes battery life.¹⁸

Pulse width, measured in μs , is the duration of a single pulse of stimulation. Pulse width ranges from 130 to 1,000 μs . There is a relationship between pulse width and output current whereby higher output currents may be needed for shorter pulse widths to ensure stimulation of the nerve. With regards to patient tolerability, it has been noted that pulse widths of 500 μs have been associated with pain in the neck, throat, or jaw and that reduction of pulse width to 250 μs alleviated these side effects in most patients.¹⁵ Reducing pulse width can also help with patients who complain of hoarseness, cough, or dyspnea.¹⁶

Finally, duty cycle refers to the percentage of time during which there is active stimulation of the nerve. Stimulation is delivered through alternating ON and OFF times. Signal ON time typically ranges from 7 to 60 seconds and OFF time from 0.2 to 180 minutes. It is recommended in the manufacturer's manual that, in a clinical setting, ON time should not exceed OFF time due to the potential risk of nerve injury.¹⁸ It should also be noted that higher duty cycles, i.e., those with shorter ON and OFF times, can be well-tolerated but tend to drain battery life more rapidly than those settings with a lower duty cycle.

Included in the VNS system is an external hand-held magnet that can be used by patients or their caregivers to deliver stimulation in the event of an aura or to attempt to stop a seizure that is already occurring. Stimulating the device with the magnet delivers a current that is often set 0.25 mA higher than the output current delivered by the VNS itself, so that the patients can feel the stimulation. The external magnet can also be used to temporarily suspend programmed stimulation for the duration that it is held over the device. This is useful for patients who would like to avoid voice alteration for performance or public speaking events as well as those whose swallowing is affected by stimulation.

Incorporating into practice

An analysis of national trends in the use of VNS for epilepsy shows that 13,218 procedures were performed between 1998 and 2005.¹⁹ In 1998, >90% of these were performed in teaching hospitals, as opposed to 75% in 2005.¹⁹ It is logical that three-quarters of VNS procedures were performed in teaching hospitals as these institutions are more likely to have a Level 3 or 4 Epilepsy Center, as previously mentioned and defined by NAEC.⁶ However, is there a trend toward VNS being performed at nonteaching hospitals? This is difficult to answer given the lack of recent data on the subject.

Consideration of the number of epilepsy patients in one's practice should also be part of this analysis. The best seizure-free rates for VNS are in the 10%–15% range.²⁰ This translates into 6–10 as the number needed to treat to get 1 seizure-free patient. If the outcome is lowered to a reasonable 5% seizure-free rate, the number needed to treat rises to about 20. In a general neurology practice with a small number of refractory epilepsy cases, aggressive use of VNS could lead to poor outcomes if adequate patient numbers are not available.

Patients with drug-resistant epilepsy who are not well-controlled after 1 year under the care of a general neurologist should be referred to a Level 3 or 4 Epilepsy Center as previously mentioned. VNS implantation should always be preceded by a comprehensive workup to ensure accurate diagnosis, exclude nonepileptic seizures, and make appropriate referral for ablative surgery if appropriate. If surgery is not an option, VNS should be considered as it is a safe and effective treatment option for patients with drug-resistant epilepsy. It is most commonly offered at a Level 3 or 4 Epilepsy Center but could also be performed in a private practice setting as mentioned above. Incorporating VNS therapy into a general neurology practice is feasible as long as proper referral patterns are in place and there is an adequate number of refractory epilepsy cases in the practice.

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