Epilepsy Treatment: Where Does VNS fit In?

When medications alone fail to control seizures, it's time to take the next step on the therapeutic ladder.

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The goal of treatment in all types of epilepsy is the same: improve the person's quality of life. Though a simple idea, there are very few studies which actually use quality of life as the primary outcome measure. Instead, seizure frequency, which is easier to measure, is used. In using this as the endpoint, the assumption is that a smaller number of seizures *equals* improved quality of life. Recent studies have demonstrated that this assumption is false. For instance, many studies have shown that the occurrence of side effects erodes a person's quality of life. Cormorbid conditions, such as depression, also significantly impact quality of life: Gilliam et al. showed that the aggressive treatment of depression in people with epilepsy directly impacted quality of life. In his study, persons who experienced little or no change in their seizure frequency reported a significantly improved quality of life when their depression was adequately addressed.[1,2]

As we have discussed previously in *Practical Neurology*, the optimal selection of an antiseizure therapy is challenging: the effectiveness of the therapy in a particular epilepsy syndrome is usually only the first step. Often, potential adverse events, the person's age and gender, and possible drug-to-drug interactions guide the selection of treatment. Comorbidities like depression clearly influence this decision: if a person has epilepsy and depression, it seems reasonable to use medications (or other therapies) that would help with *both* conditions. VNS was recently approved for use in adults with treatment-resistant depression (TRD) as well as epilepsy. Although the definition of TRD is quite specific, given the results of the study by Gilliam, VNS is often thought of as a possibility when a person has both epilepsy and depression. Encountering this problem is common, since both illnesses are present in as many as 50 percent of people with refractory epilepsy.

VNS has been available for the treatment of refractory partial epilepsy for nine years (approved by the Food and Drug Administration in 1997). Although only approved for those over age 12, there are many studies that have shown the effectiveness of VNS in children as well.[3] In fact, the long-term results in children compare favorably to the early trials in adults: 39 to 43 percent of adults were responders (responder = more than 50 percent reduction of seizures) at three years, and as many as 60 percent of children were responders at the three years' follow-up (last visit carried forward analysis).[3] The results of these trials are equal to if not better than the results of clinical trials for many antiepileptic drugs (AEDs) when studied as add-on therapy in people with refractory seizures.[4] In other words, the effectiveness of VNS as an add-on treatment seems to be comparable to AEDs. If the efficacy of these treatments is about the same, how does the physician choose: VNS or another AED?

VNS and "Refractoriness"

Before deciding when to choose VNS for refractory cases, we must first answer this question: what does the term "refractory" mean? Although frequently used and discussed, there is no universally accepted definition of this term. Simply put, "refractory" means that the illness is unlikely to respond to medication. When does this point occur—after two medicines, or four, or eight? As the list of available AEDs grows, so too does the list of possible combinations. How many combinations must be tried before the definition of "refractory" is met?

When the diagnosis of epilepsy has been made, a single medicine (monotherapy) is tried first. When this fails to control the seizures or causes side effects, a second medication may then be tried. Following this, the physician may elect to try another medication or begin a combination of therapies (polytherapy). If polytherapy fails, the chance that any combination of medications will stop the seizures is one to four percent.[5] In other words, after the first two or three trials of AEDs, it is possible to establish that the seizures are refractory. When this definition is used, up to 36 percent of people have seizures that will not respond to medication(s).[5] It is when seizures have been identified as refractory that non-medical therapies should be considered. VNS is one of these.

Patient Selection

Just as with a medication, many factors may be used to select VNS as a therapy for refractory seizures. Though only approved for use in partial epilepsies, VNS has been shown (in several case series) to be effective in generalized epilepsies as well. In fact, in the generalized epilepsies there may be even greater effectiveness[6] than was shown in the partial epilepsies. Remember that in the generalized epilepsies, there is no focal onset to the seizures. A person with this type of epilepsy would not be a candidate for resective surgery. If a person with this type of epilepsy did not respond well to initial trials of medication (and was therefore refractory), their options would be very limited. VNS offers an alternative. In short, it seems to have a broad spectrum of action.

Another question that remains unclear is this: is there another treatment with which VNS works best? Labar tried to answer this using a retrospective review of patient registry data. Unfortunately, there was no AED that stood out as working better than the others when used with VNS.

Does VNS work better before or after epilepsy surgery? The answer to this question may depend on the type of surgery. However, it seems that people who have had previous epilepsy surgery do not have as strong a response to VNS as those who are naïve to surgery. Amar performed a retrospective review of patients who had undergone a variety of surgical procedures:

there was a 50 percent reduction of seizures in the postsurgical group compared to 67 percent in the surgically naïve group. Although the response was less, the group that had surgery still experienced a reduction of seizures. In other words, VNS may remain an option if epilepsy surgery does not have the intended effect.

VNS: A Surgical Procedure

Since its approval nine years ago, there have been several VNS generator models. Models 100 (NCP 100) and Model 101 (NCP 101) are no longer produced; however, some are probably still in use. Model 100 was the initial device. Using typical settings, it had an estimated battery life of five to seven years. Model 101 was next. It extended the battery life to seven to 10 years, and reduced the volume of the generator by 33 percent. The next device was Model 102, which further reduced the size of the generator. In addition to other modifications, the new generator uses a one-prong lead, simplifying the connection between the generator and the electrode. Despite the shrinking size, the battery life continues to last from six to 11 years, assuming typical settings.[6]

Like a pacemaker, the generator is connected to a bipolar platinum wire or lead. The generator usually placed subcutaneously over the left chest wall. An alternative approach is to place the device under the left pectoralis muscle, using an incision in the left axilla. Once the generator is placed, a second incision is made over the left neck. The vagus nerve is carefully exposed, and the electrode is attached. In order to connect the leads with the generator, a "tunnel" is made from the neck incision to the chest, where the generator has been placed. The leads are connected to the generator, and the system's integrity is then tested in the operating room. Depending on the surgeon's approach, in most patients, the cosmetic appearance is excellent.

The surgery for placement of the vagus nerve stimulator can be done under either local or general anesthesia. Most surgeons prefer general anesthesia, and perform the implantation as a same-day surgery. The surgery takes about one to two hours at most, and many patients are home within several hours. For most people, the device is initiated at the first postoperative visit. That way, if there are any problems, it is easier to distinguish whether or not the difficulties are de to the surgery or to stimulation. However, the device can be initiated immediately after implantation (*e.g.*, in the operating room or recovery area). For instance, if a person lived far from the doctor's office or medical center, a decision to initiate the device immediately postoperatively would prevent a delay in starting the therapy. If the person was receiving a re-implant, the physician may decide to initiate the new device in the operating room or in the postoperative recover area. Most of the initial concerns are on surgical wound care (bleeding, infection, and incisional pain). Taken together, the risk of bleeding or infection is low, occurring in less than one percent of VNS surgeries.

Side Effects to Consider

The side effects of VNS are quite different from those attributed to AEDs. The side effects of VNS occur during stimulation. Stimulation causes voice hoarseness most often, but can also cause cough and dyspnea. Unlike most medicines, with longer duration of treatment the side effects of VNS tend to decrease. In many people, the side effects disappear over time, or become minimally apparent.

One consequence of VNS (or any implanted device) is that it may interfere with imaging studies. For instance, a person who has a VNS cannot undergo MRI of the chest, abdomen or spine. MRI of the brain (with head coils) is permitted using a 1.5 Tesla magnet. The safety of VNS with stronger magnetic fields (like the newer 3 Tesla magnets) has *not* been studied, and it is not yet known whether this can be safely performed. As these machines become more readily available, the physician must be aware of the strength of the MRI being used, if an MRI of the head is ordered.

There has always been concern that stimulation of the VNS might interrupt its normal function. One of the most important functions of the vagus is in the regulation of heart rate: more specifically, the parasympathetic fibers in the vagus nerve cause a decrease in heart rate. Because of this, there is a real concern that stimulation of the vagus would cause a slowed heart rate or possibly asystole. One important observation about the anatomy of the vagus nerve is that the nerves are asymmetric: the majority of the afferent and efferent cardiovagal fibers course through the *right* vagus nerve. This is the reason that the *left* vagus nerve was initially used for stimulation. As it turns out, the magnitude of stimulation during usual VNS settings is too small to affect the parasympathetic fibers. In other words, during normal use, VNS does not adversely affect cardiac function.[6]

"Optimal" VNS Settings

• ***Amplitude of Stimulation.*** The initial studies showed a direct relationship between the intensity of the vagal stimulation and a reduction in seizure frequency (high versus low stimulation). In the controlled trials, the range of "high dose" stimulation was defined as 1.25 mA to 1.75 mA (milliamperes). In most clinical practices, this remains the target range for treatment. However, similar to the way that medications are adjusted, some physicians have suggested that higher "doses" may have greater effectiveness. Like medications, if lower settings (*i.e.*, lower "doses") fail, the amplitude of the stimulation is increased to the maximum tolerated amount (up to 3.5 mA, the maximum the device can deliver). Although this approach is logical and reasonable, it is not known whether "doses" higher than 1.75 mA are more effective in the treatment of epilepsy. Obviously, prolonged use of higher "doses" shortens the generator's battery life.

• ***Pulsewidth.*** Although it seems evident that there is a relationship between the intensity of the electrical stimulation and a reduction in the number of seizures, less is known about how other parameters like pulsewidth affect seizures. The typical pulsewidth is 500 microseconds. Often, 250 micoseconds is better tolerated, and is commonly used. However, a very short pulsewidth of 130 microseconds is also possible. A natural question arises: which is "best"?

This answer is not entirely clear. Part of the answer is derived from studied that use electrical stimulation to depolarize a nerve. Whether or not an action potential can be generated depends on *both* the amplitude *and* duration of the electrical impulse. When a shorter impulse is used (*i.e.*, a shorter pulsewidth), higher amplitude stimulation is needed to generate the action potential. Although a setting of 250 microseconds would necessitate a slightly higher current amplitude, the difference is small. In other words, there is a small difference between 250 microseconds and 500 microseconds: if 250 microseconds is the more comfortable setting for most people, it seems logical to use this setting without worry that the effectiveness of stimulation has been compromised.[6] The same cannot be said of shorter duration pulsewidths; they are therefore not used.

• ***Frequency.*** The optimal frequency is also unclear. The usual frequency, derived from early animal studies, is 30 Hz. In some people 20 Hz is better tolerated, and is often used in the clinical setting. Settings less than 20 Hz are avoided due to concerns that low-frequency stimulation may activate parasympathetic fibers, thus causing cardiac rhythm abnormalities.

• ***Duty Cycle.*** Duty cycle is defined as: time ON / time ON + time OFF. VNS is designed to deliver intermittent stimulation. The duration of each stimulus can be adjusted, and the interval between stimulations can be changed. The usual settings are 30 seconds "on" and five minutes "off" which translates to a duty cycle of about 10 percent. Although retrospective studies have tried to answer the question of whether a higher duty is cycle is more efficacious, the answer remains somewhat unclear: there seemed to be no difference in duty cycles that included an "on" time of 30 seconds, and an "off" time of three minutes or 1.8 minutes. However, there was a small number of people who experienced a significant reduction of seizures when the "off" time was less than 1.1 minutes.[6] In other words, if the usual settings do not help to reduce seizures, higher duty cycles may be of benefit in a small percentage of patients.

• ***Battery Life and VNS Replacement.*** There are no specific guidelines as to when a generator should be re-implanted. Newer models have an elective replacement indicator (ERI). When performing a device diagnostic in the office, the ERI may signal "yes," indicating that the battery was nearing depletion. However, the ERI is not a perfect indicator as to when to re-implant: the time between ERI and actual end of battery life can be days, weeks, or months, depending on the person's VNS settings. To complicate issues, there is concern that seizure control can be lost if the VNS battery is not replaced in a timely fashion. Vonck reported two patients who had good seizure control with VNS. When their seizures worsened, indicating that the battery had been depleted, the device was replaced. Unfortunately, the seizures did not improve after the VNS was replaced.[7] In other words, it may be necessary to calculate the approximate battery life, and replace the generator *before* there is sign of failure in order to maintain good seizure control.

Conclusions

Recently, much attention has been focused on neurostimulators as a treatment for epilepsy. It is a modality that is gaining in prominence and clinical utility. However, two important questions remain: where to stimulate and how to optimize stimulation. The effect of stimulation of the vagus nerve (in several species) has been studied for decades. Studies in people with epilepsy have shown to be safe, well-tolerated and with very few surgical complications. In the United States, it is approved for use in refractory partial epilepsy in people over 12 years old. However, there are many studies which show that VNS is effective in the treatment of other types of epilepsy. In addition, it is clear that it works in children as well. After implantation, the usual settings should be tried first. Despite what is still unknown about VNS, it is clear that this therapy is an important treatment for people whose seizures do not respond to medication, and a logical step between AEDs and surgical intervention. **PN**

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