

VNS Therapy – More than just seizure reduction



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Vagus Nerve Stimulation (VNS) is a non-pharmacological therapeutic option for refractory epilepsy, with a unique mechanism of action and safety profile. In the European Union VNS Therapy is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are intractable to antiepileptic medication.

VNS Therapy delivers mild intermittent stimulation to the left vagus nerve through a pacemaker-like device implanted just under the skin in the left chest area, resulting in subsequent signals from the vagus nerve to the brain. Both patient and caregiver are able to initiate or abort stimulation by use of a hand-held magnet.

This report summarizes a presentation by Dr. Angus Wilfong, given during a series of presentations in Europe in September 2009. Dr. Wilfong reviewed the current treatment options for epilepsy, with a special focus on intractable epilepsy. The presentation was above all intended to share Dr. Wilfong's extensive clinical experience with VNS Therapy in pediatric patients.

Much of the content contained in this presentation summary is the experience of Dr. Wilfong. His outcomes are not representative of a clinical trial and do not represent statistically significant or repeatable results. Results with VNS Therapy vary from physician to physician. Dr. Wilfong is a paid consultant of Cyberonics, Inc.

Intractable epilepsy: a malignant disease

Over the years, a broad range of therapies have become available to treat epilepsy. A number of antiepileptic drugs (AEDs) are available for use in adults as well as in children. Efficacy varies by drug and by epilepsy syndrome being treated. Overall, AEDs result in seizure freedom in approximately 65% of patients. At least 35% of patients continue to have seizures despite AED therapy [1]. On average, many of these patients with inadequate seizure control have suffered for more than 20 years before being referred for non-pharmacological intervention [5].

Intractable epilepsy is generally defined as seizures that persist despite adequate trials of at least three AEDs [4]. However, in clinical practice failure to respond to the first AED is a powerful predictor of becoming intractable seizures. A large number of seizures prior to treatment also indicate a poor prognosis; in contrast, long disease duration has not shown significance as a prognostic factor.

Intractable epilepsy has a severe impact on quality of life, with consequences in many domains [6]. These include amongst others activities of daily living, independence, education and employment, interpersonal relationships and the ability to bear and raise children. Both seizures and adverse effects from AEDs can lead to cognitive impairment [6]. Patients with uncontrolled seizures show higher rates of depression [7], increased morbidity and mortality [8,9], reduced lifetime income [3] and higher health-care utilization [10]. *"Intractable epilepsy by definition does not respond to medical treatment. It tends to spread, is associated with severe disabilities, has catastrophic effects on families and even causes death. Taken together, these characteristics make intractable epilepsy a malignant disease, comparable to cancer,"* Dr. Wilfong concluded.

Management of intractable epilepsy

Thus, when considering the next treatment option in intractable epilepsy, one should not simply look at stopping as many seizures as possible, but at the same time minimizing the adverse effects from therapy. Adequate treatment also helps to prevent the psychosocial consequences of uncontrolled seizures. The goal is to maximize the patient's quality of life.

"There's always another drug that you can put your patient on, but is it likely to get your patient seizure free? Probably not. New drugs are coming and that is good, because they

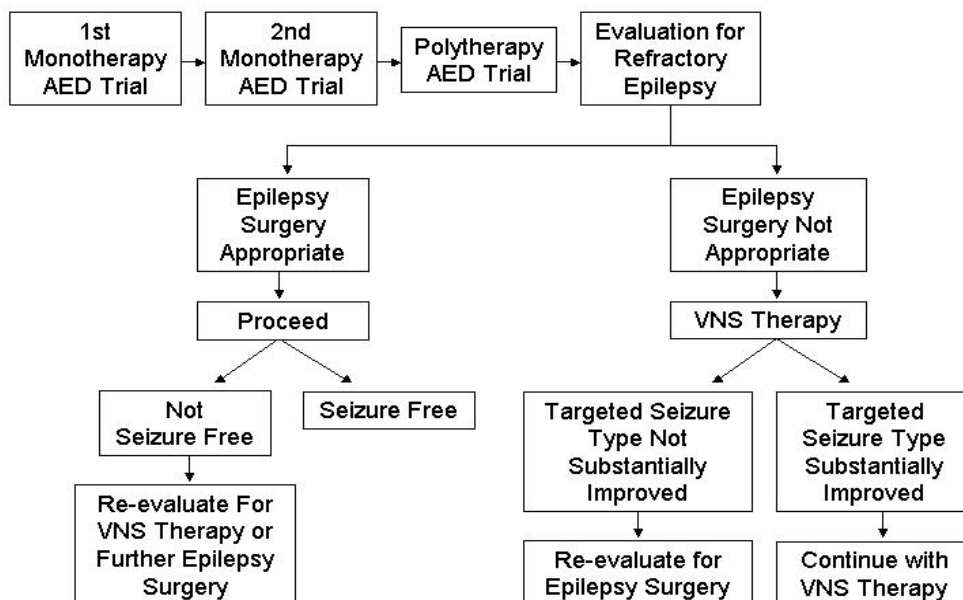
will allow us to manage the burden of seizures with less toxic side-effects, but they will not decrease the rate of intractable epilepsy."

The ketogenic diet is an adjunctive therapy primarily prescribed in children [2]. It often provides for rapid and effective seizure control, but is limited as a long-term treatment due to concerns over nutrition, growth, dyslipidemia, and tolerability. *"Most of these children will have epilepsy for the rest of their lives, so what do you do after you stop the diet, knowing that you can't put them on drugs because that's the reason why you put them on the diet?"*

Surgical therapies are reserved for patients with intractable seizures and include resective procedures for those with localization-related epilepsies and corpus callosotomy for patients with certain generalized epilepsies. In selected patients epilepsy surgery can lead to seizure freedom in approximately 70% of refractory patients [3]. However, the majority of patients will not be candidates for epilepsy surgery and some patients may refuse it.

For these patients, the introduction of VNS Therapy has provided a new surgical treatment option, which should be discussed with the patient once it's clear that he suffering from intractable epilepsy.

Treatment Sequence for VNS Therapy



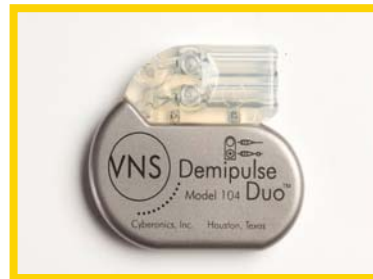
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Results with VNS Therapy improve over time

Worldwide, the VNS Therapy System has been implanted in more than 50,000 patients with epilepsy. The long-term continuation rate is high: approximately 71% of patients has been re-implanted when the battery becomes depleted [11]. The latest models of generators referred to as the Demipulse generators (Model 103 and 104, introduced in 2008), have a 48% reduction in generator thickness and a 74% reduction in generator volume compared with the earliest model 100. This adaptation has improved cosmetics, and made the device more suitable for children and adolescents. Moreover, their faster-running software has reduced the time needed in the clinic for both the interrogation and the lead test by about half. Importantly, the Demipulse software is upgradeable, which means that the patient will have the possibility of always having the latest version.



Demipulse™ Model 103



Demipulse Duo™ Model 104

Five pivotal clinical trials (E01 to E05, with varying design and inclusion criteria[7,11-16]) have established the efficacy, safety and tolerability of VNS Therapy in intractable epilepsy [7,12-16]. *"A really important overall finding is that VNS gets better with time. Whereas success of pharmacotherapy after previous drug failure in this intractable patient population is usually transient, VNS Therapy shows the opposite effect,"* Dr. Wilfong noted.

FDA approval was based on 23% overall seizure reduction after three months [17], but long-term follow-up studies have since then demonstrated much higher seizure control rates. Reported results from these studies vary from 43% of patients with $\geq 50\%$ seizure reduction at three years [17], to 52% of mean change in seizure frequency after 12 years [19]. In another study 72% median reduction in seizure frequency over 5-7 years [18] was observed. *"Results may vary from study to study, however, all these trials confirm the initial message: clinical results with VNS in epilepsy improve over time."*

“VNS Therapy in my clinical practice”

Efficacy

Contrary to the EU indication, in the USA VNS Therapy is not indicated for use in patients less than 12 years of age or for generalized seizures. Nevertheless, since 1998 Dr. Wilfong has treated over 400 children with intractable epilepsy. Many of these patients were treated off-label with VNS Therapy due to age or seizure type. His results are better than those observed in the pivotal trials. *“Today 75% of my patients are responders. Of these responders, 50% have at least a 90% reduction, and 12% have become seizure-free. My initial results were not so positive, because like you I implanted the worst-of-the-worst patients first. But the more that you use VNS Therapy, the more comfortable you are going to become and you will start using it in less severe patients. That’s when you’ll see the same high results.”*

In Dr. Wilfong’s experience patients that have responded best include those with typical and atypical absence seizures. *“20% of children that have absence seizures are intractable and these children can have a terrible life, having continuous seizures, one after another. For these patients VNS Therapy works very well.”* Other patients are children with atonic seizures, such as Lennox-Gastaut and Doose Syndrome. *“In Doose, VNS works particularly well in absences and the drops.”* In Rett syndrome, despite the autonomic instability, VNS Therapy helps both reducing intractable seizures and improves the autonomic features.

“The importance of the magnet that is part of the VNS Therapy System cannot be overemphasized,” Dr. Wilfong explained. It offers the possibility to turn on or off stimulation on demand, giving patients and their families more control over the therapy [20,21], referred to by Dr. Wilfong as “Magnetic Empowerment”. Initiating stimulation by swiping the magnet over the generator may abort seizures or decrease their severity [20-22], and may improve the post-ictal period [21]. *“This means that, for example, a child with complex partial seizures, that generalize half of the time, is now able to abort an oncoming seizure at the simple partial or aura stage of the seizure. These are outcomes that are hard to measure in clinical trials, where this child would still be a non-responder. But in daily practice it can hugely improve quality of life.”*

Tolerability and safety

VNS Therapy is well-tolerated and safe. Most side effects associated with VNS Therapy only occur during stimulation [23,24], and they generally diminish over time [24]. The most frequently reported side effects are hoarseness of the voice, paresthesia, coughing

and dyspnea [17]. These symptoms can be diminished or eliminated by adjusting the parameter settings of the VNS device [24]. By using a careful ramping procedure at the start of therapy, the occurrence of side effects is often prevented. Again, the magnet offers additional control, by offering acute relief of adverse effects by placing the magnet over the generator with tape [25]. Side effects are similar across all age groups [26,27].

With regard to safety, no idiosyncratic reactions have been reported. Because VNS is a non-pharmacological treatment, there are no drug-drug interactions and no allergic reactions. Initially, there was some concern about the potential risk for SUDEP (sudden unexpected and unexplained death in epilepsy patients) with VNS Therapy, because of the stimulation of the autonomic nervous system. However, the SUDEP rates turned out to be substantially lower in patients treated with VNS compared with patients who were candidates for epilepsy surgery [8]. *"This may be related to another big advantage of VNS Therapy: it guarantees one-hundred percent compliance,"* Dr. Wilfong stressed. This benefit is of particular relevance when treating adolescents or in other situations where complete adherence to a treatment regimen cannot always be ensured.

No pregnancy registry exists, but based on the mechanism of action of VNS Therapy there is no reason to suspect a teratogenic effect. Animal studies have shown no impaired fertility or harm to the fetus. Pregnancies in patients treated with VNS Therapy have been reported to go to term [28,29].

Points of attention with VNS Therapy

Successful treatment: patient selection

"VNS Therapy requires a different approach from other epilepsy treatments. Most doctors reserve new therapies for their worst-of-the-worst patients. These patients tend to be older and have had epilepsy for a longer period of time, and have the least likelihood of success with any treatment." Appropriate patient selection is therefore of critical importance.

Before starting VNS Therapy the treating physician should have a baseline understanding of potentially complicating comorbidities, which include obstructive sleep apnea, swallowing dysfunction, drooling or coughing. This requires adequate work-up and, if necessary, treatment for these conditions before prescribing VNS Therapy.

According to Dr. Wilfong, patients that have had epilepsy for a shorter period of time and possibly people with generalized syndromes (absence and atonic drop seizures) are the

best candidates for VNS Therapy. *"That's why children are particularly good candidates. First, a child's brain is probably more susceptible to the positive effects of stimulation than the more static nervous system of adults. And second, children have a higher proportion of generalized epilepsy than adults do."* VNS Therapy is particularly suitable for patients with multiple drug sensitivities, and in patients or families with compliance problems. For patients with simple-partial-onset seizures (auras), *"the magnet may bring tremendous benefit."*

Measuring success: setting the right expectations

Dr. Wilfong warned that expectations should be realistic. *"Because it takes time for VNS to 'kick in', I advise families not to expect any improvement for at least 6 months. Some patients do respond earlier. Although a small proportion of adults and children do attain complete freedom from seizures, the overall probability of seizure freedom is low. It is also not very likely that all medications can be stopped. But we can certainly reduce the dosage and number of drugs."*

With VNS Therapy, treatment success should not just be measured in terms of daily number of seizures. Seizures may be shorter and less intense, and the post-ictal state may be shorter. *"Even stabilizing the number of seizures over time can mean success, since without VNS this number might have doubled over time as epilepsy tends to be a progressive disorder."* Importantly, VNS Therapy has shown positive effects on behavioral outcomes as well, with children often becoming more alert and interactive.

Getting patients to respond

"Be patient," Dr. Wilfong recommended. *"Do not give up for at least 2 years."* He always uses a standard programming regimen, which starts at 0.25 mA (30 Hz, 500 μ s) for 30 seconds every 5 minutes, with magnetic activation of 0.5 mA for 60 seconds. The output current is increased by 0.25 mA each week to reach 1.5 mA. These settings are left stable for 6 months. *"Half of my patients that are seizure free are on these 'traditional setting.'" A common mistake that is often made is to ramp-up to very high doses too quickly. Just as with drugs, the risk is that you may overshoot the "sweet spot" at which a patient would respond best. More is not always better."*

Additional parameter changes must not be made more frequently than once every three months. If there is no trend towards improvement after the initial six months, the off-time is decreased every three months, to 3 minutes, 1.8 minutes, and as low as 1.1 minutes as necessary. *"If the patient is still not responding, increase the output current up to 2 mA. After that, consider a trial with alternative settings, such as longer on-time"*

(60 seconds) or lower frequency (10 Hz)." Before considering explanting, turn the generator off to ensure that the patient was in fact not responding.

Managing side effects

As mentioned most VNS side effects like cough, voice change and swallowing dysfunction are stimulation-related and improve on their own with time. *"In order to stop these side effects when speaking in public, place the magnet over the generator with tape."* If the side effects are too annoying, most improve by reducing stimulation intensity by using 20 Hz and/or 250 μ s.

Conclusion

VNS Therapy is a broad-spectrum treatment for intractable epilepsy, with many advantages over conventional therapies, in particular the magnet. VNS Therapy is effective in most patients, is safe and well-tolerated, and ensures complete treatment adherence. *"There are many different types of seizures, some not so bad, others very severe. Aggressively managing these seizures and minimizing side effects helps to maximize quality of life for patients and their families. VNS Therapy plays a critical role in my ability to help them achieve these goals,"* Dr. Wilfong concluded.

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