**ISSUE OVERVIEW**

Approximately 50 million people worldwide are affected by epilepsy, including nearly three million people in the U.S.\(^1\)\(^2\). According to the Epilepsy Foundation of America, epilepsy is the third most common neurological disorder, with approximately 200,000 new cases of epilepsy diagnosed annually; equal in prevalence to cerebral palsy, multiple sclerosis and Parkinson's disease combined. Epilepsy is associated with increased mortality: 25,000 to 50,000 people will die of seizures and related causes each year\(^2\).

Epilepsy is characterized by recurrent seizures. A seizure occurs when the electrical system of the brain malfunctions, which may cloud awareness, block normal communication and produce a variety of undirected, uncontrolled and unorganized movements\(^3\).

**The Burden of Refractory Epilepsy**

Antiepileptic drugs (AEDs) are the primary option for treating epilepsy. While many patients with epilepsy experience seizure reduction or control with AEDs, studies have shown that as many as one-third of people with epilepsy are unable to achieve seizure control with medications alone\(^4\),\(^5\).

Additionally, some combinations of multiple drugs produce side effects, such as drowsiness, lethargy, weight changes and confusion\(^6\). AEDs can also produce an increased risk of suicidal behavior for some patients\(^7\).

Epilepsy is considered drug-resistant when seizures are not adequately controlled by medications or when the side effects of the medication are intolerable and prevent patients from continuing with treatment\(^8\). Several studies have shown that the likelihood of seizure control greatly diminishes with each unsuccessful AED trial, such that after three AEDs, the chances of seizure control with the next drug is nearly zero\(^4\). In 2009, the International League

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Against Epilepsy (ILAE) published a consensus statement defining drug-resistant epilepsy as the failure of two AED trials to provide sustained freedom from seizures\(^8\).

People living with seizures that are not controlled, or with significant drug-induced side effects, face many challenges. Daily tasks, such as going to work each day or caring for a child, can be difficult or impossible for those with drug-resistant epilepsy. People with epilepsy are more likely to experience overall poorer health, unemployment, and other medical conditions when compared with the population that doesn’t have epilepsy\(^9\).

Uncontrolled seizures are associated with cognitive and memory impairment, high rates of depression, higher risk of accidental injuries and increased health care resource utilization\(^10\). These health care issues related to epilepsy – such as a broken arm during a fall or emergency room visit due to a seizure, as well as lost productivity – are costly. According to the Centers for Disease Control (CDC), epilepsy results in an estimated annual cost of $15.5 billion in medical costs and lost or reduced earnings and production\(^11\).

**VNS Therapy®**

Fortunately, non-drug treatments are available and offer many patients with drug-resistant epilepsy improved seizure control and quality of life. Cyberonics’ VNS Therapy, available in Europe since 1994 and United States Food & Drug Administration (FDA)-approved in 1997, is the only device-based treatment approved for epilepsy in the United States. VNS Therapy is approved in the U.S. as an adjunctive, or add on, therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are resistant to antiepileptic medications. In the European Union, VNS Therapy is approved 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 refractory, or resistant, to antiepileptic medications\(^12\).

VNS Therapy consists of a pacemaker-like device the size of a small watch and weighing less than one ounce. The device, or generator, is usually implanted in the left chest area during an outpatient procedure that does not involve brain surgery. A thin thread-like wire, or lead, connected to the generator, runs under the skin and is attached to the left vagus nerve in the neck. The device delivers mild, intermittently-pulsed signals to the vagus nerve, which then activates various areas of the brain. Using an external dose adjustment system, physicians

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adjust the stimulation duration, frequency and intensity. Treatment is automatically delivered at regular intervals all day, every day so treatment is automatic and continuous.

Patients and their caregivers can use an external magnet that can be briefly held over the implant site to produce an extra dose of stimulation. This extra dose can potentially shorten or stop a seizure or decrease its intensity or the recovery period.

A meta-analysis of VNS Therapy efficacy, published in the August 12, 2011 issue of Journal of Neurosurgery, evaluated 74 clinical studies with 3,321 patients suffering from drug-resistant epilepsy, implanted with VNS Therapy. Results found that, on average, approximately 50 percent of patients attained a clinically significant reduction in seizure frequency greater than 50 percent, with about 12 percent experiencing a 90 percent decrease in seizures.\(^\text{13}\)

Another study of 436 patients with drug-resistant epilepsy found that VNS Therapy, when used as part of a multimodality treatment plan, resulted in an at least 50 percent reduction in seizures for more than 60 percent of patients. In some cases, more than 40 percent of patients experienced at least a 75 percent reduction in seizures.\(^\text{14}\)

Additionally, studies have shown that the efficacy of VNS Therapy typically improves over time.\(^\text{15,16}\)

Earlier addition of non-drug treatments such as VNS Therapy may result in better outcomes for patients with drug-resistant epilepsy. Research has shown that VNS Therapy can be effective even when used after unsuccessful epilepsy brain surgery.\(^\text{17}\)

The increased seizure control that most VNS Therapy patients experience can lead to improved overall health and quality of life. In a 2011-published study conducted by Emory School of Medicine researchers, an evaluation of 1,655 patients with drug-resistant epilepsy showed that with the addition of VNS Therapy, patients experienced a lower occurrence of epilepsy-related conditions, injuries and other health issues. Additionally, hospitalizations and emergency room visits significantly decreased following treatment with VNS Therapy, and benefits were sustained over time. As a result of reduced patient healthcare utilization and comorbidities, the study showed VNS Therapy to be associated with significant, long-term healthcare cost savings beginning 18 months after implantation.\(^\text{10}\)


\(^\text{15}\) Elliot, R.E., et. al. Efficacy of vagus nerve stimulation over time: Review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS >10 years. Epilepsy & Behavior. 2011, 3: 478-483


The side effects associated with VNS Therapy are typically mild to moderate, usually occur during stimulation and often diminish over time. These side effects may include voice alteration, tickling in the throat, cough and a feeling of shortness of breath. Additionally, because it is a non-drug treatment, VNS Therapy is sometimes considered an attractive treatment option for women who are pregnant or wish to become pregnant. Although the safety and effectiveness of VNS Therapy have not been specifically studied in pregnant women, healthy, full-term births have been reported with VNS Therapy. In addition, studies have not shown any harm to the fetus.

Most patients treated with VNS Therapy continue receiving the treatment long-term. Ninety-seven percent of patients continue with VNS Therapy after one year, and 72 percent after three years.

**Focused on Device Solutions for Epilepsy**

VNS Therapy has been used to treat more than 70,000 patients worldwide to date.

- Cyberonics continues to focus on the development of VNS Therapy and other device solutions for epilepsy. In February 2011, Cyberonics announced FDA approval of AspireHC®, the fifth generation of VNS Therapy® technology. AspireHC incorporates special features and functionality for the benefit of patients and their physicians, including enhanced battery life, electronics and features that simplify programming. The AspireHC is particularly beneficial for patients that require higher stimulation parameters.

Cyberonics remains committed to developing device-based solutions to help people with epilepsy gain better control of their seizures and enjoy a higher quality of life and health.

For more information about VNS Therapy or Cyberonics, Inc., please visit [www.cyberonics.com](http://www.cyberonics.com) or contact [Cyberonicsepilepsy@schwartzmsl.com](mailto:Cyberonicsepilepsy@schwartzmsl.com).

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