New research sheds light on VNS Therapy mechanism of action

Recent articles provide insight into the mechanisms of action of VNS Therapy and how substance P may provide a biological marker for treatment-resistant depression (TRD).

VNS Therapy mechanism of action

Two of the studies involved preclinical research to elucidate the molecular mechanisms underlying the therapeutic action of VNS Therapy. A study from the University of Cagliari, Sardinia, Italy, found that acute vagus nerve stimulation in rats increased the expression of brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), and nerve growth factor in the hippocampus and cerebral cortex; decreased the abundance of nerve growth factor mRNA in the hippocampus; and, like the antidepressant drug venlafaxine, increased the norepinephrine concentration in the prefrontal cortex.¹ This study demonstrates that acute vagus nerve stimulation triggers neurochemical and molecular changes in the rat brain involving neurotransmitters and growth factors known to play a crucial role in neuronal trophism. It also provides insight into molecular mechanisms underlying the mechanism of action of VNS Therapy in both epilepsy and TRD.

A team at the University of Texas Health Science Center in San Antonio, Texas, used immunohistochemistry for biomarkers of short-term (c-Fos) and long-term (ΔFosB) neuronal activation to map regions in the brain activated by acute (2 h) or chronic (3 weeks) VNS in conscious rats.² Acute VNS significantly increased c-Fos staining in the nucleus of the solitary tract, paraventricular nucleus of the hypothalamus, parabrachial nucleus, ventral bed nucleus of the stria terminalis, and locus coeruleus, but not in the cingulate cortex or dorsal raphe nucleus (DRN). Acute VNS did not affect ΔFosB staining in any region. Chronic VNS significantly increased ΔFosB and c-Fos staining bilaterally in the regions affected by acute VNS, as well as in the cingulate cortex and DRN. In addition, the researchers compared VNS Therapy with desipramine in the forced swim test (FST), a widely used behavioral test for detecting antidepressant-like activity. While both desipramine and VNS significantly decreased immobility in the FST (thereby demonstrating antidepressant activity), the two treatments showed different effects: desipramine decreased immobility by increasing climbing behavior, and VNS decreased immobility by increasing swimming behavior. This study, then, identified actual brain sites where VNS may produce its clinical effects.

Substance P and TRD

A group at Butler Hospital, Brown University, Providence, Rhode Island, investigated the role of the neuropeptide substance P in the etiology of major depression.³ A few studies have shown that CSF concentrations of substance P are higher in unmedicated depressed patients than in healthy controls and that these levels are unchanged by antidepressant treatment. This research used CSF samples obtained via lumbar puncture in 19 medication-free healthy controls and 19 patients receiving psychotropic medications for TRD. Mean substance P concentration was significantly lower in the medicated patients with TRD, and 10–12 weeks of VNS Therapy did not change the CSF substance P concentrations significantly. This suggests that low substance P may serve as a biological marker for severe, chronic TRD.

INSIDE!

• Coming soon! The new VNS Therapy Demipulse™ generator
• Gretchen: A VNS Therapy case history
• More about VNS Therapy dosing
• Bibliography

Dosing VNS Therapy

Since the approval of VNS Therapy for TRD, more than 1,600 psychiatrists now have treated more than 3,000 patients. As the result of this, experience-based information regarding dosing strategies for VNS Therapy has emerged. Here are some basic guidelines.

Recommended initial dose settings
The VNS Therapy Depression Physician’s Manual recommends a waiting period of ≥2 weeks after implant procedure prior to initial dose setting. Here are the parameters most commonly used at this first dosing visit:

- 0.25 mA output current
- 30 Hz frequency
- 500 µs pulse width
- ON 30 seconds
- OFF 5 min
- 0.0 mA magnet mode output current

Next steps
After the initial office visit, dosing sessions typically follow these guidelines:

- Increase output current in increments of 0.25 mA, or as tolerated
- Increasing output current in increments of 0.25 mA allows the physician to achieve the maximum tolerated dose for each patient
- If the patient doesn’t tolerate increased output current, reducing the pulse width to 250 µs may help keep the patient more comfortable
- Frequent office visits (every 2–4 weeks) are suggested for the first several months to monitor patient response and adjust device parameters
- The median stimulation parameters used at 12 months during the pivotal study were: output current at 1.0 mA, 20 Hz frequency, 500 µs frequency, 30 seconds ON time, and 5 minutes OFF time
- Most psychiatrists attempt to achieve output current levels between 1.0 and 1.5 mA
- Some patients will accommodate to stimulation levels over time and should therefore tolerate further increases (in 0.25-mA steps) in output current, if needed

- Consider adjusting the duty cycle to achieve additional efficacy after about 9 months of active stimulation. Adjustments to duty cycle should be less frequent than the initial adjustments to output current. The most frequently used initial approach to duty cycle adjustment is reducing the OFF time from 5 minutes to 3 minutes:
  - Once a patient responds to VNS Therapy, no further changes are necessary

What are the most important things to remember when adjusting VNS Therapy dosing?

- Monitor the patient for tolerability. Be aware of side effects, such as shortness of breath, coughing, throat tightness/discomfort, excessive hoarseness, and discomfort with swallowing
- Ensure the patient can tolerate settings before leaving the office
- Follow the guidelines in the VNS Therapy Physician’s Manual
- After reaching a maximum tolerated dose over several dosing sessions, give the patient time (3–6 months) to adjust to parameter settings before making additional adjustments. If patient responds during this time, no further changes are necessary
- Record each dose adjustment in the patient’s chart
Gretchen Grappone: a VNS Therapy case history

Patient history

• Age: 35 years
• Diagnosis: Major depressive episode
• Duration of illness: 21 years
• Symptoms: Loss of interest in usual activities, loss of appetite and concentration, insomnia, social avoidance, morning lethargy
• Went on disability in 1995

Medication and treatment history

• Over 20 medications and combinations without relief
• 54 sessions of ECT: initially effective, but with diminishing results
• VNS Therapy since February 2001

Outcomes

• First sign of efficacy: Insomnia relieved after 3–4 months of VNS Therapy
• Gradual mood improvement
• With psychiatrist, gradual elimination of all medications
• Returned to work as a research coordinator and trainer at the NH-Dartmouth Psychiatric Research Center
• Now pursuing a master’s degree in social work
• Married in September 2005

This case history is an example of results with VNS Therapy. Individual treatment results will vary.

VNS Therapy™ is a trademark of Cyberonics, Inc.
Bibliography

•A review of STAR*D: It defined the prevalence of treatment-resistant depression and is a model for further practical clinical outcomes studies

•See page 2

•See page 2

•See page 2

•Magnetic resonance spectroscopy results suggested there might be damage and loss of neurons, as well as abnormality in membrane phospholipid-associated metabolism, in the thalamus of patients with TRD

Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within-versus across-class switches. Biol Psychiatry. 2007; [Epub ahead of print].
•A metanalysis suggests a modest yet statistically significant advantage in remission rates when switching patients with SSRI-resistant depression to a non-SSRI rather than an SSRI antidepressant

•The most effective treatment strategies for TRD promote patient compliance using agents with a low rate of premature discontinuation and early therapy change. Managed care providers could benefit from a customizable model evaluating the overall cost-effectiveness of different strategies against TRD

•Ways to improve long-term treatment outcomes for depressed primary care patients, focusing on:
  – Improving antidepressant treatment adherence
  – Treatment guidelines and step-wise treatment algorithms
  – Barriers to effective treatment and how to overcome them

To speak with a Regional Case Manager about patients in your practice who may benefit from VNS Therapy, call 1-877-669-4867 to learn more about how we can work with you to verify your patients’ insurance benefits.
**Brief Summary of Safety Information for the VNS Therapy™ System**

**Epilepsy and Depression Indications** (March 2007)

### INTENDED USE / INDICATIONS

The VNS Therapy System is intended for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that have been refractory to additional antiepileptic drugs. The VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

### WARNINGS — DEPRESSION

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new-onset sleep apnea in patients who have not previously been diagnosed with this disorder.

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause unconsciousness. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation.

### WARNINGS — EPILEPSY

The VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should continue to have ongoing care and ongoing engagement in seizure-control activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others.

Sudden unexplained death in epilepsy (SUDEP). Through August 99, 10 sudden and unexpected deaths were reported to Cyberonics involving 11 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 days after the initial or replacement implantation. Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound is performed elsewhere, patients should be given antibiotics.