New research begins to show why VNS Therapy works when other antidepressant treatments have failed

New insight into VNS Therapy and its unique mechanism of action

New research may begin to explain why VNS Therapy works in patients whose depression has not responded to multiple antidepressant treatments. In a peer-reviewed article in the August 2006 Journal of Pharmacology and Experimental Therapeutics, Dr. Adrienne E. Dorr and the late Dr. Guy Debonnel of McGill University, Montréal, describe the effect in rats of long-term vagus nerve stimulation (VNS) on firing rates in the dorsal raphe nucleus (DRN) and the locus coeruleus (LC), two areas of the brain involved in mood regulation. Known antidepressant drugs typically decrease the firing rates in one or both of these brain areas acutely, but over time the firing rates recover back toward baseline. This phenomenon is related to changes in the levels of the neurotransmitters serotonin (emanating from the DRN) and norepinephrine (emanating from the LC).

In the study, 1 to 3 days of VNS had slight effect vs sham-operated controls, while long-term treatment (14, 21 and 90 days) increased activity significantly in both brain areas. This increase continued over time, a pattern that reflects the improvement experienced by patients receiving VNS Therapy for treatment-resistant depression (TRD).

Dr. Debonnel commented in August 2006, “This research begins to provide insight into why VNS Therapy has proved beneficial for patients with TRD when other antidepressant treatments were ineffective.”

This work was supported by the Canadian Institute of Health Research and Cyberonics, Inc.

STAR*D: Long-term outcomes of standard treatment strategies in TRD

A paper, “Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report,” in the November 2006 issue of the American Journal of Psychiatry found that for patients with TRD remission rates declined as the number of treatments increased. The article, by a team of authors led by A. John Rush, MD, of the University of Texas Southwestern Medical Center, Dallas, summarized the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

Sponsored by the National Institute of Mental Health, STAR*D is the largest and longest study ever to evaluate depression treatments. It focused on remission, rather than response.

The paper described 4 levels involving a total of 11 possible treatments. Patients who did not reach remission or who could not tolerate treatments were encouraged to proceed to the next treatment step. Patients who achieved remission or a meaningful improvement with acceptable tolerability could enter a 12-month naturalistic follow-up phase.

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Compiled rates of remission, intolerance, and relapse

Remission was defined as a score of ≤5 on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16) at acute exit; a QIDS-SR16 of ≥11 defined relapse. Intolerance was defined as the proportion of participants who left the level prior to 4 weeks for any reason and those who left thereafter whose exit form indicated intolerance. The relapse rate was the proportion of subjects relapsing of those who made at least 1 postbaseline call to the interactive voice response system. Treatment step pairwise comparisons showed only Step 1 to be significantly different from the rest (P<0.0001).

The calculated cumulative remission rate after 4 acute treatment trials was 67%. Importantly, however, patients who required more treatment steps had higher relapse rates during a 12-month naturalistic follow-up phase. Intolerance rates also increased with each treatment step.


Reimbursement updates

Medicare and Medicaid

Cyberonics has submitted a formal request to the Centers for Medicare & Medicaid Services (CMS) to amend its current coverage policy for VNS Therapy to include appropriate patients with TRD.

During the 30-day CMS public comment period last fall, CMS received more than 1300 comments supporting access to VNS Therapy for TRD. Comments in favor of coverage for TRD came from:

- More than 250 psychiatrists with extensive experience in the diagnosis and treatment of TRD
- The American Psychiatric Association
- More than 650 patients and family members with personal experience with TRD
- Some 40 patient advocacy organizations, including the National Alliance on Mental Illness (NAMI), the Depression and Bipolar Support Alliance (DBSA), the Mental Health America (formerly the National Mental Health Association), and the American Society for Suicide Prevention
- 175 healthcare professionals, including neurologists, surgeons, nurses, social workers, and health economists
- 20 members of Congress

This is an ongoing process. CMS is expected to post a draft national coverage decision early this year, followed by an additional 30-day comment period and a final decision in May.

Private insurance

“Will my insurance pay for it?” is one of the most commonly asked questions in the VNS Therapy Phone Facts Sessions, the bimonthly teleconferences for people interested in VNS Therapy. On a case-by-case basis, the answer is often eventually positive.

VNS Therapy is the only treatment FDA-approved for the long-term treatment of chronic or recurrent TRD. As of December 11, 2006, 269 payers have approved individual case-by-case coverage, and over 2000 patients with TRD have begun VNS Therapy. To find out whether a specific payer has provided coverage, go to www.vnsthery.com/CaseApprovals.asp.
Bibliography

Recent publications


• A patient with TRD and chronic low back pain that remitted with VNS Therapy retained acute pain sensitivity to laboratory thermal pain procedures during VNS Therapy


• VNS Therapy and ECT can be used safely and effectively either sequentially or concurrently


• See page 1 for description


• Review of the use of VNS Therapy for TRD: mechanism of action, efficacy, safety, and history of its use


• Level 4 of the STAR*D trial found low rates of response for medication changes after 3 previous medication treatments


• Level 3 of the STAR*D trial found low rates of response with augmentation strategies after 2 previous medication treatments


• See page 1 for description

From the 19th Annual U.S. Psychiatric & Mental Health Congress
November 16–19, 2006
New Orleans, Louisiana


• All 6 patients with TRD and chronic pain treated with VNS Therapy reported improved depressive symptoms and reduced chronic pain

Beckett Thurman L, Dabiri B. Parameters of vagus nerve stimulation (VNS) therapy in treatment-resistant depression: a review of data from ten patients. Abstract.

• Patient records indicate dosing strategies that maximize efficacy and tolerability


• A high percentage of patients with TRD who showed substantial clinical benefit after 3 and 12 months of VNS Therapy maintained the improvement at 24 months

Cohen LJ, Bunker MT. Economic implications of vagus nerve stimulation therapy for treatment-resistant depression. Abstract.

• A mathematical model based on remission and response rates from clinical studies of VNS Therapy predicts substantial cost savings

Warnell RL, Elahi N. Introduction of vagus nerve stimulation therapy into a maintenance ECT regimen: a case study and cost analysis. Abstract.

• A patient receiving VNS Therapy for bipolar disorder successfully discontinued maintenance ECT, with estimated cost savings of $2350–$3750 over 10 months of VNS Therapy (prorated)
Updates on initiatives

TRD Registry to provide insights into depression, VNS Therapy

The TRD Registry, the first registry specifically for patients with TRD, will provide unprecedented insight into long-term outcomes. By collecting comprehensive data from ≥2000 patients over 2 to 5 years, the TRD Registry will support rigorous analyses and substantially improve the understanding of TRD and available treatments. Up to 100 sites will participate in the registry.

By following the clinical course and outcome for patients with TRD treated with and without adjunctive VNS Therapy, the TRD Registry will generate data supporting numerous peer-reviewed publications.

As of November 17, 2006, 37 sites have enrolled 202 patients with TRD: 174 will receive VNS Therapy (76 have begun treatment) and 28 will receive treatments other than VNS Therapy.

The Registry collects assessments that measure factors such as severity of depression, quality of life, psychosocial impairment, history of healthcare, history of trauma, sexual functioning, medication usage, and side-effect burden.

To learn more about this ground-breaking study, call 1-281-228-7269, send an e-mail to Registry@TRDRegistry.org, or visit www.TRDRegistry.org.

TRD Outcomes: postapproval assessment of VNS Therapy — Now with faxable forms

TRD Outcomes is a real-time outcomes assessment designed to collect outcomes and summarize aggregate results of early post-approval experience with VNS Therapy in TRD.

TRD Outcomes will provide real-world insight and experience to assist you and your patients in making treatment decisions. If you’re a psychiatrist using VNS Therapy for TRD, you’re invited to participate and help build this early experience outcomes database.

Physicians supply baseline data on patients before initiating VNS Therapy and provide outcomes updates at 3, 6, and 12 months. As of November 22, 2006, 104 psychiatrists have entered baseline characteristics for 215 patients, 3-month data for 78 patients, and 6-month data for 38 patients.

Now faxable data entry forms make participation more convenient. These new forms can go directly into your patient’s chart. To participate, contact your Cyberonics nurse case manager or therapeutic consultant. The data collection process is compliant with relevant patient privacy laws.

Faxable forms for TRD Outcomes

Baseline characteristics of TRD Outcomes patients are similar to those of patients enrolled in the pivotal study for VNS Therapy. Watch for more information from TRD Outcomes in the next issue of this newsletter.

VNS Therapy dosing study update

A Cyberonics-sponsored, multicenter, double-blind, randomized dosing study is comparing the safety and effectiveness of VNS Therapy administered at various doses for the treatment of patients with TRD.

Approximately 460 patients will participate in this study at up to 30 sites. As of November 15, 2006, 25 study sites nationwide have enrolled 86 patients.

To learn more about this study, please contact your VNS Therapy case manager, or go to www.clinicaltrials.gov/ct/show/NCT00305565. Please refer to this study by ClinicalTrials.gov identifier NCT00305565.
Comprehensive VNS Therapy support services

• Patient education materials, including brochures and an educational video, contain important information for patients considering VNS Therapy

• Experienced, licensed nurse case managers provide reimbursement support and VNS Therapy education

• IVEA forms facilitate insurance and patient education support

New and updated

• Portraits of Hope: 33 patients and 8 leading psychiatrists recount their experiences with VNS Therapy

For materials to distribute to your patients, please contact your VNS Therapy case manager or therapeutic consultant.

VNS Therapy
Phone Facts Sessions

• Informational teleconferences for people interested in VNS Therapy moderated by psychiatrists
• Includes interviews with patients receiving VNS Therapy
• The 1st and 3rd Tuesday of every month
  • 7:00 PM Central Time
  • 1-866-598-9336

www.VNSTherapy.com provides information about TRD and VNS Therapy for physicians and patients. Includes an assessment tool, patient testimonials, patient and physician manuals, newsletters, IVEA forms, and more

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VNS06-21-1000-2
1. INTENDED USE / INDICATIONS: DEPRESSION (USA)

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years and older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

2. CONTRAINDICATIONS

The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.

Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

3. WARNINGS

Physicians should inform patients about all potential risks and adverse events discussed in the Physician's Manual (Depression). This document is not intended to serve as a substitute for the complete Physician's Manual (Depression).

This device is a permanent implant. It is only to be used by patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed after patients and physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted in patients who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression.

The safety and efficacy of the VNS Therapy System have not been established for uses not covered in the "Intended Use/Indications" section of the Physician's Manuals (Depression and Epilepsy).

Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or dose changes.

The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathways) have not been established. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

It is important to follow recommended implantation procedures and intraoperative product testing described in the Physician's Manual (Depression). During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia, orystole occurs restimulation or inspection, or a clinically significant change in heart rate is encountered during a System Diagnostics or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration.

Shortness of breath (dyspnea) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea.

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency to a tolerance that does not cause excessive 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 should be ruled out by restimulation or direct current stimulation. Either event could cause nerve damage. 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.

Patients with the VNS Therapy System or any part of the VNS Therapy System implanted should not have full body MRI.

Use of the Magnet to activate stimulation is not recommended for patients with depression. Excessive stimulation at an excessive duty cycle has resulted in degenerative nerve damage in laboratory animals.

Patients who manipulate the Pulse Generator and Lead through the skin may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

4. PRECAUTIONS

Physicians should inform patients about all potential risks and adverse events discussed in the Physician's Manual (Depression).

Prescribing physicians should be experienced in the diagnosis and treatment of depression and should be familiar with the programming and use of the VNS Therapy System.

Physicians who implant the VNS Therapy System should be experienced in the surgical technique of bipolar vagotomy.

Physicians should be familiar with vagus nerve anatomy, particularly the cardiac branches; and they should be trained in the surgical technique relating to the implantation of the VNS Therapy System.

The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS Therapy should be used during pregnancy only if clearly needed.

The VNS Therapy System is indicated for use only in the left vagus nerve in the neck area inside the carotid sheath.

The VNS Therapy System is indicated for use only in the left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve.

It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient can use a neck brace for the first week to help prevent infection.

The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillator therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device.

Reversal of Lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that Leads with dual connector pins are correctly inserted (white marker band/serial number to + connection) into the Lead connectors.

The patient can use a neck brace for the first week to help prevent infection.

Do not program the VNS Therapy System to an “ON” or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.

Do not use frequencies of 5 Hz or below for long-term stimulation.

Resetting the Pulse Generator turns the device OFF (output current = 0 mA), and all device history information is lost. Patients who smoke may have an increase risk of laryngeal irritation.

5. ENVIRONMENTAL AND MEDICAL THERAPY HAZARDS

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a Pulse Generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation. VNS Therapy System operation should always be checked by performing device diagnostics after any of the procedures mentioned in the Physician’s Manual (Depression). For clear imaging, patients may need to be specially positioned for mammography procedures because of the location of the Pulse Generator in the chest.

Therapeutic radiation may damage the Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately. External defibrillation may damage the Pulse Generator. Use of electroconvulsive therapy (ECT) and magnetic resonance imaging (MRI) ablation devices may damage the Pulse Generator.

Magnetic resonance imaging (MRI) should not be performed on a patient with a VNS Therapy System. The heat induced in the Lead by an MRI body scan can cause injury. If an MRI should be done, use only a transmit-and-receive type of head coil. MRI compatibility was determined using a 1.5T General Electric Signa scanner with a Model 100 only. When other MRI systems are used, adverse events may occur because of different magnetic field distributions. Consider other imaging modalities when appropriate.

Procedures in which the radiofrequency (RF) is transmitted by a body coil should not be done on a patient who has the VNS Therapy System. This protocol must not be used which utilize local coils that are RF-receive only, with RF-transmit performed by the body coil. Note that some RF head coils are receive only, and that most other local coils, such as knee and spinal coils, are also RF-receive only. These coils must not be used in patients with the VNS Therapy System.

Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound is required, avoid positioning the area of the body where the Pulse Generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning is not possible or avoided, program the Pulse Generator output to 0 mA for the treatment, and then after therapy, reprogram the Pulse Generator to the original parameters.

Routine therapeutic ultrasound could damage the Pulse Generator and may be inadvertently concentrated by the device, causing harm to the patient.

For information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, please refer to the Physician's Manual (Depression) for complete information.

6. ADVERSE EVENTS

Implant-related adverse events reported during the pivotal study in ≥5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypopharynx, dyspnea, nausea, headache, neck pain, and syncope with or without other electrochemical symptoms such as paresthesia or cough. Stimulation-related adverse events reported during the acute sham-controlled study by ≥5% of VNS-Therapy-treated patients are listed in order of decreasing occurrence: voice alteration, increased dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea, and incision pain.

Cyberonics, Inc.
100 Cyberonics Boulevard
Houston, Texas 77018 USA
Tel: 281-228-7200 / 800-332-1375
Fax: 281-218-9332
www.VNSTherapy.com

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(Copies of VNS Therapy Physician’s and Patient’s Manuals are posted at www.VNSTherapy.com/manuals). The information is not intended to serve as a substitute for the complete and thorough understanding of the material presented in all of the Physician’s Manuals for the VNS Therapy System and its component parts, nor does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

USA Depression: Summary 20-0006-1100W
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Brief Summary of Safety Information for the VNS Therapy™ System (Depression Indication) July 2005