From May 19 to 24, 2007, thousands of psychiatrists at the annual meeting of the American Psychiatric Association (APA) in San Diego, California, had the opportunity to learn more about TRD and the role of VNS Therapy.

Vagus nerve stimulation

On May 20, “Caring for Our Most Challenging Patients with Depression: An Interactive Forum on Novel Treatments” discussed treatments using brain stimulation: some treatments already approved for use in TRD (like VNS Therapy) and others still under investigation. Chaired by Charles B. Nemeroff, MD, PhD, of the Emory University School of Medicine, Atlanta, Georgia, the symposium enabled participants to identify criteria used to recognize patients with TRD, and compared and contrasted somatic interventions for TRD (including VNS Therapy). This symposium was sponsored by the APA and by an educational grant from Cyberonics, Inc.

A continuing medical education course on May 20 addressed the growing interest in the use of VNS Therapy for mood disorders and other conditions. Directed by Ziad H. Nahas, MD, of the Medical University of South Carolina, Charleston, this course reviewed the anatomy of the vagus nerve and described how stimulating it may affect mood and other symptoms of depression. Participants also learned about the effects of VNS Therapy on depression and other neuropsychiatric conditions. During a hands-on workshop as part of the course, psychiatrists learned dosing strategies for VNS Therapy.

TRD and STAR*D

Other APA symposia featured reports from the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Sponsored by the National Institute of Mental Health, STAR*D is the largest and longest study ever to evaluate depression treatments.

Several meetings presented recent information from STAR*D. “Insights from STAR*D: Are Our Patients’ Needs Being Met?” took place on Saturday, May 19. Chaired by Maurizio Fava, MD, of the Massachusetts General Hospital, Boston, this symposium enabled practitioners to identify the unmet needs of patients who are unlikely to achieve remission with any one treatment; evaluate strategies for partial or non-responders that include switching, augmentation, and combination strategies; and design a treatment plan that utilizes nonpharmacologic together with pharmacologic strategies to achieve remission.

“STAR*D Findings: Implications for Patients, Clinicians, and Other Stakeholders,” chaired by Grayson S. Norquist, MD, of the University of Mississippi Medical Center, presented key findings from Levels 1–4 of STAR*D. During this symposium, K. Ranga Krishnan, MD, of the Duke University Medical Center, discussed “The Role of Other Treatment Options in Managing Depression,” including VNS Therapy.

INSIDE!

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Employer-funded plans

More and more employers with self-funded health care plans have approved case-by-case coverage for VNS Therapy after their health plans have denied coverage. In self-funded plans, employers or unions pay a substantial portion of the cost of medical expenses for their employees. More than 85 million people in the US are covered by self-funded plans. Your patient’s human resources department can tell whether his or her health care plan is self-funded.

If your patient’s health care coverage is a self-funded plan and your appeals have not succeeded in obtaining coverage for VNS Therapy for TRD, your patient may wish to meet with his or her employer’s benefits manager. The Cyberonics prior authorization case manager working with you and your patient can provide materials that will help during this process. The documentation your patient will need may include a letter of medical necessity from you that states:

- The FDA-approved indication for VNS Therapy: The adjunctive long-term treatment of chronic or recurrent depression in a patient ≥ 18 years of age experiencing a major depressive episode who has not had an adequate response to ≥ 4 adequate antidepressant treatments
- The duration of illness
- Detailed documentation of previous treatments:
  - The names of medications
  - The dose, the date and duration of the trial
  - The reason each drug was stopped (was it ineffective or not tolerated?)
  - The use of outpatient psychotherapy
- Other health care utilization:
  - ECT or ECT refusal
  - Hospitalizations related to depression
  - Costs of treatment for this patient’s depression

The VNS Therapy appeals packet

Cyberonics nurse case managers can assist you and your patient in pursuing coverage. Cyberonics has developed a packet of materials to help patients talk to their employer’s benefits department about overturning their health plans’ denial of coverage for VNS Therapy for TRD.

The appeals packet includes the following materials:
- A checklist for patients that outlines the materials they need to present to their employers
- A discussion guide to help patients talk to their employers about the impact of TRD on their life and work
- An educational brochure for employers that includes information about TRD and its impact on employers and employees, as well as information about VNS Therapy
- Contact information for the case management team if the employer has additional questions that the patient would like Cyberonics to address

A decision from CMS

The Centers for Medicare and Medicaid Services (CMS) has confirmed its preliminary determination not to provide national coverage for VNS Therapy as a treatment for Medicare beneficiaries who have TRD. During the two public comment periods, more than 98% of the 2,732 comments submitted to CMS were in favor of coverage of VNS Therapy for patients with TRD. We want to thank the many patients, potential patients, physicians, organizations and others who took the time to comment. Cyberonics will continue to support psychiatrists and patients who are pursuing coverage of this treatment.

As we evaluate all the options available to optimize access of VNS Therapy in TRD, we intend to work with CMS and other interested parties to understand the additional evidence they desire to extend coverage. The body of evidence supporting VNS Therapy in TRD continues to grow, and we plan to share that evidence with CMS, as well as with other payers, as it becomes available.

Since the approval of VNS Therapy for TRD, over 300 payers have provided coverage for more than 3,000 patients on a case-by-case basis. Several local and regional plans have issued coverage policies for VNS Therapy in TRD.
Managing patient expectations

VNS Therapy works over time

It’s important to note that after 1 year, 1 out of 3 patients receiving VNS Therapy in the pivotal study experienced significant improvement, and many patients who did not respond immediately to VNS Therapy did experience improvement over time. Therefore, managing patient expectations through this process is key.

VNS Therapy works differently from other treatments for depression. Patients should understand that their response to VNS Therapy may be gradual. Unlike other treatments for depression, VNS Therapy provides a remarkable durability of response.

Important points to discuss with patients

- VNS Therapy works gradually, improving over time
- Many people who do not respond immediately to VNS Therapy do show improvement later
- Some people experience mood improvements within the first 2 months; for others, the benefits develop gradually over time
- Improvement may be so gradual that friends and family members observe it before the patient does
- Most people who respond to VNS Therapy maintain their improvement long term
- Many patients experience improvement in important quality-of-life areas

Patient education support

To assist with patient education, you can refer patients to the Connections program, which provides telephone support from nurse case managers. In addition, bimonthly psychiatrist‐moderated teleconferences enable patients to hear from a person receiving VNS Therapy and ask questions anonymously.


Lisa: A VNS Therapy case history

Patient history

- 37‐year‐old female
- Duration of illness: >20 years
- Hospitalized once for severe depression
- Diagnosis: major depressive episode
- On disability due to severe depression

Treatment history

- Sertraline 200 mg, bupropion 300 mg, trazodone 100 mg, ziprasidone 160 mg, alprazolam 1.5 mg
- 10 ECT sessions—no improvement, short‐term memory loss
- Psychotherapy every 2 weeks: July 2002—July 2003; July 2004—present
- VNS Therapy prescribed in August 2005

Coverage process

- Patient’s primary health care plan denied coverage through initial submission and subsequent plan appeals
- Patient was on short‐term disability leave from a company with a self‐funded plan
- Patient appealed denial of coverage through her company’s Employee Assistance Program
- Employer determined that costs associated with VNS Therapy procedure should be covered in December 2005

Implanted with VNS Therapy—December 2005

Outcomes

- Patient’s mood improved within 2 weeks
- Patient returned to work in January 2006
- Current remission sustained ≥1 year
- Patient has returned to college after 19 years, pursuing a major in business administration
- Current medications: sertraline 150 mg (decreasing 50 mg every month), bupropion 300 mg, ziprasidone 160 mg, alprazolam 1.0 mg

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


- 10 weeks of VNS Therapy was associated with an increase in intracortical inhibition, suggesting that VNS Therapy can change motor cortical excitability in patients with depression


- PET scans of patients receiving VNS Therapy reveal evolving changes in brain metabolism along the pathway of the vagus nerve and in regions involved in responses to other mood disorder treatments


- A review of brain stimulation techniques used in psychiatry


- Indications, proposed mechanism of action, potential perioperative complications during placement of the VNS Therapy device, and anesthetic considerations for patients receiving VNS Therapy


- Dosing strategies


- VNS Therapy is associated with ventro-medial prefrontal cortex deactivation corresponding to the antidepressant response


- A case report

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The information contained in this Brief Summary for Physicians represents partial excerpts of important information concerning the use of this product, potential safety complications, or efficacy outcomes. Prescribing physicians should be experienced in the diagnosis and treatment of depression or epilepsy and should be familiar with the programming and use of the VNS Therapy System.

Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to 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.

VNS Therapy is indicated 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 are refractory to antiepileptic medications.

Depression (US)—The VNS Therapy System is indicated for the adjunctive long-term treatment of chemotherapy- or recurrence-related depression in patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more different antidepressant treatments.

2. CONTRAINDICATIONS

Vagotomy—The VNS Therapy System cannot be used in patients after a bilateral or left vagal nerve vagotomy.

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

3. WARNINGS — GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the physician’s manuals. This document is not intended to serve as a substitute for the complete physician’s manuals.

The safety and efficacy of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entrant pathways) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

Postoperative bradycardia can occur among patients with certain underlying cardiac abnormalities. It is important to follow recommended implantation procedures and intraoperative product testing described in the Implantation Procedure part of the physician’s manuals. During the intraoperative System Diagnostics (lead test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate is encountered during System Diagnostics (Lead Tests) or during initiation of VNS therapy, the system 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 swallowing difficulties that are at greatest risk for aspiration.

Dyspnea, cough, or shortness of breath 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 or prolonging "OFF" time may prevent exacerbation of apnea.

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause the patient to malfunction or the patient or the Lead 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 a full body MRI.

Excessive stimulation at an excess duty cycle (that is, one that occurs when “ON” time is greater than “OFF” time) has led to degenerative nerve damage in laboratory animal studies.

Patients who manipulate the Pulse Generator and Lead through the skin (Twiddler’s Syndrome) may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the device. To prevent excessive stimulation, the Pulse Generator should be set to OFF (output current = 0.0 mA) immediately.

4. WARNINGS — EPILEPSY

The VNS Therapy System should only be monitored and programmed by physicians who have specific training and expertise in the management of seizures and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

The VNS Therapy System is not curative. Physicians should warn patients that the VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should be instructed to inform the Magnastim manufacturer if they suspect a malfunction, and then to contact their physician immediately for further evaluation.

The VNS Therapy System may damage or disrupt the Lead from the Pulse Generator and/or possibly cause damage to the device. To prevent excessive stimulation, the Pulse Generator should be set to OFF (output current = 0.0 mA) immediately.

5. WARNINGS — DEPRESSION

This device is a permanent implant. It is only to be used on patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by 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 by physicians 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.

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 drug dosage changes.

Excessive stimulation. Note: Use of the Magnet to activate stimulation is not recommended for patients with depression.

6. PRECAUTIONS — GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System and its companion parts or does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

1 The information contained in this Brief Summary for Physicians represents partial excerpts of important information concerning the use of this product, potential safety complications, or efficacy outcomes. Prescribing physicians should be experienced in the diagnosis and treatment of depression or epilepsy and should be familiar with the programming and use of the VNS Therapy System.