

# VNS Therapy™ connections™

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

### New insight into why VNS Therapy works differently

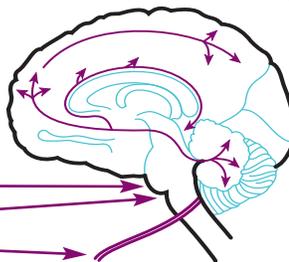
New research may help explain why VNS Therapy works in patients whose depression has not responded to multiple antidepressant treatments. An article in the August 2006 *Journal of Pharmacology and Experimental Therapeutics* describes the effect of VNS Therapy on 2 areas of the brain that affect levels of the neurotransmitters norepinephrine and serotonin.<sup>1</sup>

In the study, VNS Therapy increased activity in both brain areas. This increase continued over time, a pattern that reflects the improvement experienced by patients receiving VNS Therapy. With medications, the timing is different: activity in one or both of these brain areas changes over the short term, but then often reverts back to the original level.

Drs. Adrienne E. Dorr and Guy Debonnel wrote the article. Dr. Debonnel commented, "This research begins to provide insight into why VNS Therapy has proved beneficial for patients with treatment-resistant depression (TRD) when other antidepressant treatments were ineffective."

### Brain areas affected by VNS Therapy

Raphe nuclei  
Locus coeruleus  
Vagus nerve



### New options needed in treatment-resistant depression (TRD), studies demonstrate

What are the most effective treatments for people whose depression does not respond to antidepressant treatments? Finding answers to this question is the goal of the ongoing 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. It focuses on remission—getting people well.<sup>2</sup>

In August 2006, the *American Journal of Psychiatry* reported STAR\*D results for 235 people with depression that had not responded to two previous antidepressant regimens. The study found that switching to another antidepressant after two unsuccessful treatments resulted in remission rates of less than 20%.<sup>3</sup>

An earlier study, not part of STAR\*D, appeared in the May 2006 *Journal of Clinical Psychiatry*. It looked at 1- and 2-year results for standard antidepressant treatments in 124 people with treatment-resistant depression (TRD). The research team, headed by Dr. David L. Dunner, found remission rates under 10%.<sup>4</sup> The rate of sustained remission (from 1 to 2 years) was also low.

These two studies highlight the need for people with TRD to discuss additional treatment options with their doctors.

Please see page 3 for references to these articles.

### INSIDE!

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- Ask the doctor
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### Meet Janet, a VNS Therapy patient

When Janet first received the diagnosis of severe clinical depression in 1997 at the age of 41, she was surprised and shocked. She also felt extreme guilt, shame, and disconnection from her husband and son. For a period of time Janet tried a variety of medications and was hospitalized several times. She became frustrated with the ineffectiveness of the medications and concerned about the side effects. ECT was effective for her but its benefits wore off over time.

A few years passed when eventually her life spiraled downward. Janet said, "I felt as though my spirit was suffocating." In 2002, unable to cope with her circumstances and suffering from the cognitive distortions of depression, Janet attempted suicide by throwing herself in front of an oncoming train. Remarkably, she survived the attempt although it cost her the loss of her left leg. She is still not sure how she got through this difficult time, except for her faith and love from family and friends.

When another relapse occurred in July 2005, Janet's psychiatrist told her about VNS Therapy. After receiving information, much consideration, and listening to a VNS patient teleconference, Janet received VNS Therapy in November 2005. She first noticed changes about 6 months later.

Now after 8 months, Janet says VNS Therapy helps her assimilate knowledge; heightens her ability to cope with stress at work as a phone operator and receptionist; and improves her overall quality of life and appreciation for the little things in everyday living.

"Finally," Janet says, "I can appreciate the world and its more beautiful gifts, as if a light has been turned on. For example, my husband and I were driving home without air conditioning after a long work day, very hot and tired, when I noticed a small sparrow fly under the eaves of a funeral home. I saw she was building a nest to create new life. In the location she had chosen, I thought this was so sweet, and without thinking, I expressed my delight out loud. Immediately I felt surprised that I would even bother to say something about what I had seen.

I finally feel as though my spirit can breathe again."



*I finally feel as though my spirit can breathe again.*

### Ask a VNS Therapy patient

#### What are some specific things you do now that you couldn't do before you had VNS Therapy?

**Helen:** Before I had VNS Therapy, I couldn't get out of bed, couldn't function, and didn't want to talk to or see anyone. When I began VNS Therapy in February 2006, my mood changed instantly. I feel great and am no longer depressed. I can do the simple things now that I once took for granted. I'm getting back into social circles, contemplating dating, talking to my kids, and making it through my workday without the degree of stress I used to feel. VNS Therapy has truly changed my life—I can smile and mean it now. Hope is finally a reality.

#### What steps did you take to get insurance coverage for VNS Therapy?

**Lisa:** Initially, my insurer denied coverage for VNS Therapy for TRD. I worked closely with my case manager at Cyberonics during the appeals process. She helped me get through the process day by day. Ultimately, my employer helped me override the insurer's decision. I scheduled my VNS Therapy procedure 10 days after I received the approval. Now, I've been depression-free for 3 months.

### Mark your calendar

- **October 5:** National Depression Screening Day
- **October 21:** The Depression and Bipolar Support Alliance 2006 conference at Chicago-O'Hare Airport has the theme Living Well: Making Recovery Real. A unique opportunity to discover recovery strategies to help you get and stay well. For more information, go to [www.dbsalliance.org/Conference/Conference.html](http://www.dbsalliance.org/Conference/Conference.html).

NOTE: The testimonials in this document are only examples of VNS Therapy results. Individual treatment results will vary.



**Ask the doctor**

**Darin Dougherty, MD**

Assistant Professor of Psychiatry  
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**What dose gives the greatest efficacy?**

In the clinical trials of VNS Therapy in TRD, the median value at 1 year was 1.0 mA (milliamperes) for output current. The median value for how long the pulse lasted was 30 seconds. The median time between pulses was 5 minutes.<sup>5</sup>

However, there is no single dose setting that works for everybody, just as there is no medication dose that works for everybody. Some people may notice improvements at lower doses while other people may experience improvements only at higher doses. All people start with a current setting of 0.25 mA when the VNS Therapy pulse generator is first turned on. Most people are sent home from this initial visit at this setting. However, some people may not notice any side effects at 0.25 mA and the doctor may elect to increase the dose to 0.50 mA or higher during this initial visit; this is the exception, however. After the person adjusts to the dose setting from the initial visit (usually 0.25 mA), the doctor increases the dose by another 0.25 mA every 2–3 weeks over the next 6–8 weeks or so with the goal of achieving a target dose of 1.0 mA. Increasing the current by 0.25 mA at a time allows the psychiatrist to achieve the most appropriate dose for each person while minimizing possible side effects.

The 1.0-mA target dose is based on the dose settings used in the clinical trials of VNS Therapy. The doctor then monitors the person's progress with VNS Therapy over the next several months and changes the dosage depending on his or her outcome. After a person reaches either the maximum tolerated dose or desired level of improvement, no further changes may be necessary. However, the dose can be increased further if there is a lack of clinical response. The most important things to remember are that peoples' responses to different dose settings will vary considerably, and that doctors and patients should work together to find the correct dose setting for each individual.<sup>5</sup>



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**Connections: a VNS Therapy resource program for you**

- Brochures
- Live phone conferences—VNS Therapy Phone Facts Sessions
  - Hear from a patient about his or her experience with VNS Therapy
  - Listen to a psychiatrist experienced with VNS Therapy
  - Tuesdays, October 3 and 17, November 7 and 21
  - 7:00 PM Central Time
  - Call TOLL-FREE 1-866-598-9336
- Nurse case managers who can answer your questions about VNS Therapy and help with insurance benefits verification
- For more information, call **1-877-NOW-4VNS** (1-877-669-4867) or visit [www.VNSTherapy.com](http://www.VNSTherapy.com)



**Autumn antidepressant tip**

Do you have trouble remembering which medication to take when? Try a 7-day pillbox with separate compartments for morning, noon, and night, available at most drugstores.



**References:** **1.** Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *J Pharmacol Exp Therapeut.* 2006;318:890-898. **2.** Questions and Answers about the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Study — Background. Available at: [http://www.nimh.nih.gov/healthinformation/stard\\_qa\\_general.cfm](http://www.nimh.nih.gov/healthinformation/stard_qa_general.cfm). **3.** Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: A STAR\*D report. *Am J Psychiatry.* 2006;163:1161-1172. **4.** Dunner DL, Rush AJ, Russell JM, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry.* 2006;67:688-695. **5.** *Depression Physician's Manual. VNS Therapy™ Pulse Model 102 Generator and VNS Therapy™ Pulse Duo Model 102R Generator.* Houston, Tex: Cyberonics, Inc.; December 2005.

Please see the full indication and safety information enclosed.

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## SAFETY INFORMATION FOR THE VNS THERAPY™ SYSTEM\*

### INTENDED USE/INDICATIONS – UNITED STATES

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for 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 adequate antidepressant treatments.

### 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 the VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

### WARNINGS

This device is a permanent implant. It is only to be used in 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 inform patients about all potential risks and adverse events discussed in the VNS Therapy System *Physician's Manual*, including information 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 dose changes.

Patients who have pre-existing swallowing, cardiac, or respiratory difficulties (including, but not limited to, obstructive sleep apnea and chronic pulmonary disease) should discuss with their physicians whether VNS Therapy is appropriate for them since there is the possibility that stimulation might worsen their condition. Patients with the VNS Therapy System or any part of the VNS Therapy System implanted should not have full body MRI.

### ADVERSE EVENTS

The most commonly reported ( $\geq 10\%$ ) side effects from stimulation included hoarseness, increased cough, neck pain, dyspnea (shortness of breath), dysphagia (difficulty swallowing), paresthesia (prickling feeling in the skin), and laryngismus (sore throat). The most commonly reported ( $\geq 10\%$ ) side effects from the implant procedure included incision pain, hoarseness, incision site reaction, device site pain, device site reaction, pharyngitis (sore throat), dysphagia, and hypesthesia (numbness).

\*THE INFORMATION CONTAINED IN THIS SUMMARY REPRESENTS PARTIAL EXCERPTS OF IMPORTANT PRESCRIBING INFORMATION TAKEN FROM THE PRODUCT LABELING. THE INFORMATION IS NOT INTENDED TO SERVE AS A SUBSTITUTE FOR A COMPLETE AND THOROUGH UNDERSTANDING OF THE VNS THERAPY SYSTEM, NOR DOES THIS INFORMATION REPRESENT FULL DISCLOSURE OF ALL PERTINENT INFORMATION CONCERNING THE USE OF THIS PRODUCT. (CAUTION: U.S. FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN.)