



PATIENT'S GUIDE for Depression

October 2017

RxOnly

This Patient's Guide is a supplement to the physician's manuals. It is not intended to substitute for advice from your doctor. For a complete discussion of indications for use, contraindications, precautions, warnings, and potential side effects, talk to your doctor.



Your doctor is your first source for health-related questions and information. Liva Nova cannot provide healthcare advice or services.

Your doctor's phone number: _____

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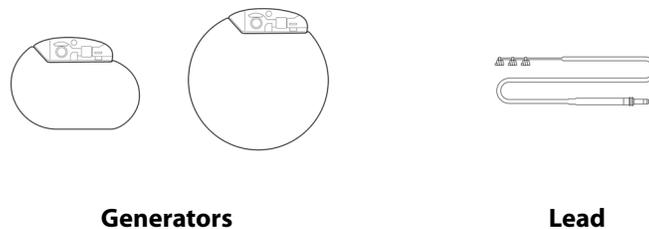
1 Introduction to VNS Therapy[®]

Many people have depression. Through the years, doctors and scientists have learned much about depression. They have developed drugs and other treatments. Despite these efforts, some people still have depression. Your doctor has proposed the VNS Therapy System for you to reduce the symptoms of your depression because other treatments have failed to control them adequately.

The VNS Therapy System sends a mild electrical impulse to a nerve that goes to the brain. This nerve is called the vagus nerve. The treatment is Vagus Nerve Stimulation (VNS) Therapy (VNS Therapy[®]).

1.1 Implantable Parts of the VNS Therapy System

Figure 1. Implantable Parts



Generator

The main implantable part is the VNS Therapy generator, sometimes called a stimulator. The generator is computer controlled and battery powered. It sends signals through the electrodes of the lead to the brain through the left vagus nerve in the neck.

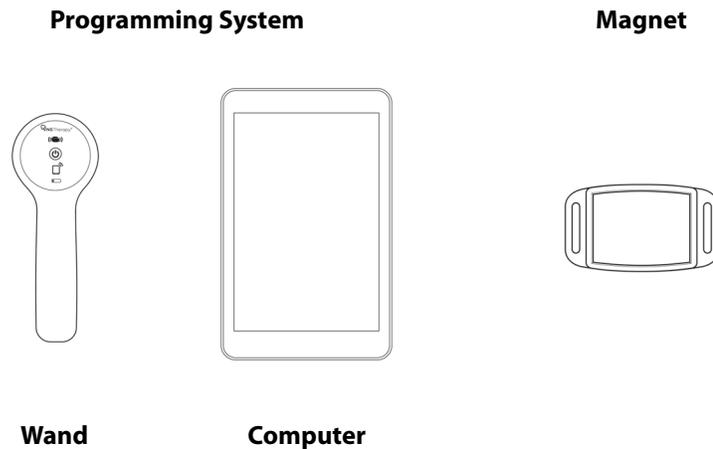
The generators have many settings. Your doctor will choose the settings for your generator. He or she can change the periodic stimulation at any time with the programming system. Most of the time, changing the settings is a painless procedure, takes only a few minutes, and can be done in your doctor's office.

Lead

The lead connects the generator to the vagus nerve.

1.2 Nonimplantable Parts of the VNS Therapy System

Figure 2. Nonimplantable Parts



Programming System

The Programming System includes the programming wand and programming computer with pre-installed software.

Magnet

Your doctor provides a magnet for you to stop stimulation if and when you need to.

i **Note:** See “How to Handle the VNS Therapy Magnets” on page 15.

2 Who Uses VNS Therapy?

VNS Therapy has been approved for people with chronic or recurrent treatment resistant depression who have failed to respond to four or more adequate treatments. It is *not right* for everyone who has depression. You and your doctor will decide if VNS Therapy is right for you. Your doctor will also decide if you have any other medical conditions that might be affected by VNS Therapy.

2.1 Indications for Use

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.

2.2 Contraindications

VNS Therapy should not be used (is contraindicated) in the following situations or procedures:

- **Left vagotomy** — The VNS Therapy System should not be used in people who have had the left vagus nerve cut to treat another disorder (a left vagotomy).

- **Diathermy** — Inform anyone treating you that you CANNOT have any short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy anywhere on your body because you have an implanted VNS Therapy System. Injury or damage can occur during diathermy treatment whether your VNS Therapy System is turned “ON” or “OFF.”

 **Note:** Diagnostic ultrasound is not included in this contraindication.

Diathermy is a treatment to promote healing or relieve pain. It is provided by special medical equipment in a doctor's office, dentist's office, or other healthcare setting.

Energy from diathermy therapy may cause heating of the VNS Therapy System. The heating of the VNS Therapy System resulting from diathermy can cause temporary or permanent nerve, tissue, or blood vessel damage. This damage may result in pain or discomfort, loss of vocal cord function, or possible death if blood vessels are damaged.

Diathermy may also damage parts of your VNS Therapy System. This damage can result in loss of therapy from your VNS Therapy System. More surgery may be required to remove or replace parts of your implanted device.

3 **Benefits of VNS Therapy**

 **Note:** See “Overview of Clinical Studies” on page 24 for a description of the D-02 study.

The effectiveness of VNS Therapy in decreasing depressive symptoms was primarily demonstrated by improved scores on standardized tests after 12 months and 24 months of VNS Therapy in the D-02 study.

3.1 **Effectiveness Results From the D-02 Clinical Study**

3.1.1 **Three-month results**

At the end of the first 3 months, the proportion of patients who had at least a 50% reduction in depression symptoms was 15% in the group of patients receiving active stimulation, slightly better than for patients who were not receiving stimulation (10% of these patients had at least a 50% reduction in symptoms). This finding suggested that the full effects of VNS Therapy might require more than 3 months of treatment.

 **Note:** See Table 1.

3.1.2 **One-year results**

After 1 year of VNS Therapy, the results showed that 30% of the study patients were responders (at least a 50% improvement in depressive symptoms) and 17% were remitters (minimal to no depressive symptoms). The results from a second rating scale of depression symptoms showed that 22% of the group were responders and 15% were remitters, and the results from a third rating scale showed that 32% were responders and 23% were remitters. It should be noted that about one in four or five people who were implanted with the device during the study were not included in these calculations of success at 12 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

i Note: See Table 1.

3.1.3 Two-year results

After 2 years of VNS Therapy, the results showed that 32% of the patients were responders and 17% were remitters. The results from a second rating scale of depression symptoms showed that 27% of the group were responders and 13% were remitters. It should be noted that about one in three people who were implanted with the device during the study were not included in these calculations of success at 24 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

i Note: See Table 1.

Table 1. Percent of Responders and Remitters After VNS Therapy

Standardized Test	HRSD ₂₄		IDS-SR ₃₀		MADRS	
	Responders	Remitters	Responders	Remitters	Responders	Remitters
3 mos	15%	7%	14%	6%	17%	10%
12 mos	30%	17%	22%	15%	32%	23%
24 mos	32%	17%	27%	13%	N/A	N/A

Responders - ≥ 50% improvement in depressive symptoms.

Remitters – minimal to no depressive symptoms.

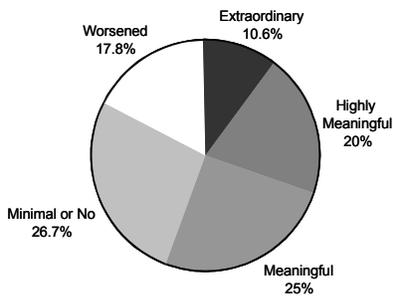
3.1.4 Additional categorization of clinical benefit

After 12 months of VNS Therapy, the patients were also assessed to categorize the degree of improvement in their depression symptoms. The amount of improvement was categorized as follows:

- **Worsened** – depressive symptoms worse than when VNS Therapy was started
- **Minimal to no change** – 0% to 24% improvement in depressive symptoms
- **Meaningful clinical benefit** – 25% to 49% improvement in depressive symptoms
- **Highly meaningful clinical benefit** – 50% to 74% improvement in depressive symptoms
- **Extraordinary clinical benefit** – over 75% improvement in depressive symptoms

Figure 3 shows the percentage of patients who were in the different categories after 12 months of VNS Therapy. It should be noted that about one in four people who were implanted with the device during the study were not included in these calculations of success at 12 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results shown in the figure.

Figure 3. Categories of Clinical Benefit After 12 Months of VNS Therapy (HRSD₂₄)



i **Note:** 56 percent of patients experienced at least a meaningful clinical benefit after 12 months of adjunctive VNS Therapy.

3.1.5 Maintenance of benefit over time

Although less than one in three or one in four patients (depending on the rating scale used) appeared to respond to VNS Therapy, most—but not all—of those patients continued to be responders over time. For example, among the 30 patients who were responders on the HRSD₂₄ rating after their first 3 months of VNS Therapy, 60% continued to be responders after one year of VNS Therapy, and 70% were responders after two years of VNS Therapy. Among the 54 patients who were responders after 12 months of VNS Therapy, 69% continued to be responders after two years of VNS Therapy.

3.2 Quality of Life Measurements in the D-02 Clinical Study

In addition to improvements in depressive symptoms, patients who received VNS Therapy for one year in the D-02 study reported improvements in quality of life.

3.3 Expected Rate of Response to VNS Therapy

For patients in whom VNS Therapy is effective, the benefits are not always seen right away. In fact, the 12-week acute studies did not show a significant difference between patients receiving VNS Therapy and those who were not receiving it. Depressive symptoms may improve slowly over the first year of treatment.

3.4 Treatment Continuation Rates

Not all patients continue on VNS Therapy. During the D-02 study, 92% of the patients continued to receive therapy at 12 months and 82% continued to receive therapy at 24 months.

3.5 Limitations of VNS Therapy

VNS Therapy has not been shown to cure depression. It does not work for everyone. For most patients in whom it is effective, improvement in depressive symptoms will be slow. Some patients may have no change in symptoms with VNS Therapy, and some may actually get worse while receiving VNS Therapy. At present, doctors have no way to predict which patients will respond to VNS Therapy.

i **Note:** See “Expected Rate of Response to VNS Therapy” on page 8.

4 Warnings and Precautions

As with all types of treatment for depression, VNS Therapy carries some risks. Talk to your physician about the following warnings, precautions, side effects, and hazards. Ask about other risks not covered in this manual that you should know about.

4.1 Warnings

4.1.1 General Warnings

- **Use** — 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.
- **Worsening depression/suicidality** — You will need to be observed closely for clinical worsening and suicidal thoughts or behavior (suicidality), especially at the time of drug or drug dose changes, or VNS Therapy stimulation parameter changes.
- **Unapproved uses** — The safety and efficacy of the VNS Therapy System have not been established for uses outside its approved indications for use. The safety and efficacy of VNS Therapy *have not* been shown for people with these conditions:
 - ◆ Acute suicidal thinking or behavior
 - ◆ History of schizophrenia, schizoaffective disorder or delusional disorders
 - ◆ History of rapid cycling bipolar disorder
 - ◆ History of previous therapeutic brain surgery or brain injury
 - ◆ Progressive neurological diseases other than epilepsy or depression
 - ◆ Irregular heart beats (Heart arrhythmias) or other heart abnormalities
 - ◆ History of dysautonomias
 - ◆ History of lung diseases or disorders, including shortness of breath and asthma
 - ◆ History of ulcers (gastric, duodenal, or other)
 - ◆ History of fainting (vasovagal syncope)
 - ◆ Only one vagus nerve
 - ◆ Other concurrent forms of brain stimulation
 - ◆ Preexisting hoarseness
- **Swallowing difficulties** — Difficulty swallowing may occur with active stimulation, and aspiration may result from the increased swallowing difficulties.
- **Shortness of breath** — Shortness of breath may occur with active VNS Therapy, especially if you have chronic obstructive pulmonary disease or asthma.
- **Obstructive sleep apnea** — Use of the VNS Therapy device can cause or worsen pre-existing obstructive sleep apnea (episodes where breathing stops for short periods of time

while sleeping). See your physician if you show any signs or symptoms of obstructive sleep apnea or worsening obstructive sleep apnea.

- **Device malfunction** — Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems.
- **Device removal** — Removal of the VNS Therapy System requires an additional surgical procedure. When a device is removed, the surgeon may leave part of the lead behind. This may pose certain risks. See “Medical Hazards” on page 11.
- **Device manipulation** — Do not manipulate the generator and lead through the skin, as this may damage or disconnect the lead from the generator and/or possibly cause damage to the vagus nerve.

4.1.2 Magnetic Resonance Imaging Warnings

- **Before having any MRI performed** — **Call your doctor, so your VNS Therapy System can be discussed with the MRI personnel.** In many cases an MRI can be performed safely under certain conditions. However, for a few other cases, surgery may be required to remove the VNS Therapy System prior to an MRI. *Before* undergoing an MRI scan, the VNS system diagnostic information will be collected and the current turned off. The current will be turned on again after the scan is completed. Your doctor has access to detailed MRI-related information in the physician’s manual.
- **MR Unsafe**  — The VNS Therapy patient magnet is **MR Unsafe**. *Do not* carry the patient magnet into the MR scanner room. The magnet could become a dangerous flying object if attracted by the strong magnetic field of the MRI scanner.
- **Pain or other sensation during MRI scan** — If, during an MRI scan, you have any pain, discomfort, heating, or other unusual sensations, notify the MRI operator, so the MR procedure can be stopped, if necessary.
- **Questions?** — **Call your doctor** if you have questions about having an MRI scan.

4.2 Precautions

4.2.1 All Generator Models

- **Use during pregnancy** — The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy.
- **Laryngeal irritation may result from stimulation** — Patients who smoke may have an increased risk of laryngeal irritation.

4.2.2 Model 1000 Only

- **Day-Night Programming** — The optional Day-Night Programming feature does not automatically adjust for Day Light Savings Time or time zone changes. If you're using this feature, you will need to go back to your doctor for reprogramming of the generator for any time changes.

5 Hazards

5.1 Environmental Hazards

Being close to certain types of equipment can affect the generator. Move away from or avoid equipment such as transmitting antennas.

- **Pacemaker Warning signs** — Talk to your doctor before going into places with Pacemaker Warning signs.
- **Small appliances** — Properly operating microwave ovens and other small electrical appliances, such as toasters, hair dryers, and electric shavers, *should not affect* the generator.
- **Cellular phones** — Cellular phones can affect some implanted cardiac defibrillators and pacemakers, but tests to date show that they *do not affect* the generator.
- **Transmitting devices** — Properly operating electrical ignition systems and power transmission lines *should not affect* the generator. Sources with high energy levels, such as transmitting antennas, *may interfere* with the device. Move at least 1.8 meters (6 feet) away from any equipment that interferes with your device.
- **Antitheft devices, airport security systems, and other metal detectors** — Antitheft devices and metal detectors *should not affect* the generator or be affected by it. As a precaution, however, move through them at a steady pace; do not linger in the area and stay at least 40 centimeters (16 inches) away from such equipment.
- **Electronic Article Surveillance (EAS) System tag deactivators** — The tag deactivators found in many retail stores can interfere with VNS Therapy when it is used near the generator. It can cause accidental activations or stop pulses. Stay at least 60 centimeters (2 feet) away from tag deactivators to avoid potential interference.
- **Devices with strong electromagnetic fields** — Electrical or electromechanical devices with a strong static or pulsing magnetic field can cause the generator to start suddenly. Such devices may include strong magnets, tablet computers and their covers, hair clippers, vibrators, antitheft tag deactivators, and loudspeakers. Keep this type of equipment at least 20 centimeters (8 inches) away from your chest. If your generator stops while you are in a strong electromagnetic field, move away from the source so the device may return to regular operation.

5.2 Medical Hazards

Medical equipment, procedures, and surgery using certain electrical instruments can affect the VNS Therapy System's operation and sometimes damage the generator or lead.



Make sure that medical personnel know you have a device implanted in your chest.



Always call your doctor before you have any medical tests that may affect, or be affected by, the VNS Therapy System as described. Precautions may be needed.

- **Routine diagnostic procedures** — Most routine diagnostic procedures, such as diagnostic ultrasound and radiography (x-rays), *should not affect* the VNS Therapy System.

- **Mammography** — Because the generator is in your chest, you may need to be specially positioned for a mammogram. Otherwise, the device may be seen as a shadow on the mammogram. It could make a lesion or lump in that area hard or even impossible to detect. Make sure that your doctor and the mammography technician are aware of the implanted device.
- **Radiation treatment** — Treatment with radiation, cobalt machines, and linear accelerators *may damage* the generator. No testing has been done to date. The effect of radiation on the device is not known. Talk with your doctor if you plan to have radiation treatment.
- **Other procedures** — External cardiac defibrillation and other procedures for heart problems, as well as extracorporeal shockwave lithotripsy, diathermy, and electrocautery, *may damage* the generator. If you had any of these procedures and your doctor did not know about it, have the generator checked. While *diagnostic* ultrasound *should not affect* the VNS Therapy System, *therapeutic* ultrasound therapy *could damage* the generator or inadvertently harm you.

5.3 Interference with Other Devices

While the generator is stimulating or being set or tested, it may briefly interfere with nearby equipment. If this happens, move at least 1.8 meters (6 feet) away from such equipment.

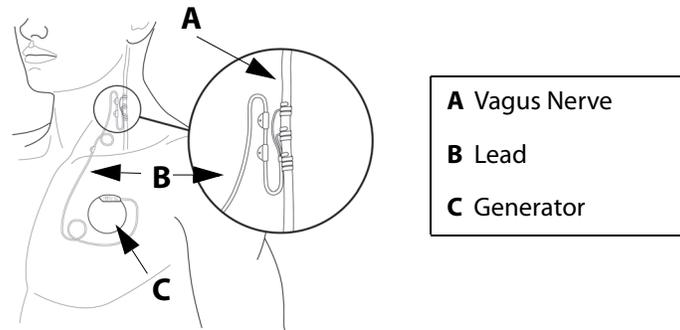
- **Radios and hearing aids** — The generator can interfere with devices that operate in the 30 kHz to 100 kHz range. Hearing aids and transistor radios operate in this range. In theory, the generator could affect them, but no effects have yet been reported. No detailed testing has been done, so the effects are unknown.
- **Implanted devices** — The generator may affect other implanted medical devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems. These could lead to inappropriate responses from the generator.
- **Credit cards and computer disks** — The VNS Therapy magnets are very strong. They *can damage* televisions, computer disks, credit cards, and other items that are affected by strong magnetic fields. Keep your magnet at least 25 centimeters (10 inches) away from any of these items. **Do not carry or store the magnets near them.**

6 Implant Surgery

VNS Therapy requires surgical placement of the pulse generator and lead by a surgeon. At follow-up office visits, your doctor checks the settings and changes them as needed.

6.1 Placement of the Generator and Lead

The generator is placed under the skin of the upper chest. The lead is attached to the vagus nerve on the left side of the neck, and runs under the skin to connect to the generator. See Figure 4.

Figure 4. Implant Location

6.2 Surgery

The implant surgery lasts from about 1 to 2 hours and typically involves general anesthesia, although local anesthesia is sometimes used. You may stay in the hospital overnight.

The surgeon makes a small incision on the left side of the neck and a second incision below the collarbone in the chest or armpit. The lead is passed under the skin between the two incisions. The surgeon attaches the lead to the left vagus nerve in the neck and then plugs the other end of the lead into the generator. The generator is placed in the “pocket” created at the site of the incision below the collarbone. Finally, the surgeon closes the incisions. See Figure 4. The operation can be reversed if you and your doctor ever decide to have the VNS Therapy System removed. Removal of the pulse generator and/or lead requires another surgical procedure.

 Sometimes when a surgeon removes a VNS Therapy System, the surgeon will decide to leave a portion of the lead behind in order not to risk damaging the vagus nerve. This may pose certain risks (see “Medical Hazards” on page 11).

7 Follow Up After Surgery

The generator is usually turned on 2 weeks after it is implanted. Your doctor will program the generator to the proper settings for you. At that office visit and at subsequent visits, your doctor will check the VNS Therapy System. Your doctor will make sure that it is working well and that the treatment is comfortable for you. Tell your doctor at your next visit if you no longer feel the routine stimulation. Your doctor may decide to change your settings.

 It is recommended that you see your doctor **at least once every 6 months. Your doctor will check the VNS Therapy System for safe and effective operation.**

You will be given an Implant and Warranty Registration Form, which has information about your generator and lead.

You will also receive a Patient Implant Card, which has details about your generator and lead, your physician name and number, and other information needed in case of a device-related emergency.



Carry the Patient Emergency Information Card at all times.

Consider registering with an emergency service such as MedicAlert® Foundation (www.medicalert.org) so information about the VNS Therapy System will be available to hospital and emergency response personnel when needed. If you have questions about the MedicAlert Foundation, discuss it with your doctor.

7.1 Antidepressant Medications

Most patients treated with VNS Therapy in the clinical studies also continued to take antidepressant medications. A significant number of patients had new medications added or doses of their old medications increased during the studies.

Your doctor may advise you to continue to take your antidepressant medications after you begin receiving VNS Therapy. Your doctor may also decide to add new medications to your treatment. Always follow your doctor's instructions regarding your medications.

7.2 After Treatment Begins

7.2.1 Common Side Effects

Call your doctor right away if any of the following occur:

- Your voice is constantly hoarse.
- Stimulation becomes painful or irregular.
- Stimulation causes any choking, trouble with breathing, trouble with swallowing, or change in heart rate.
- You or someone else notices changes in your level of consciousness (for example, you become constantly drowsy).
- You think that the generator may not be stimulating properly or that the VNS Therapy System battery is depleted (stops stimulating).
- You notice anything new or unusual that you relate to the stimulation.



Note: See "Device Complications" on page 17.

- The feeling that you usually have during stimulation becomes stronger or weaker.
- Your depressive symptoms increase or suicidality (suicidal thoughts or behavior) increases.



Note: See "Additional Safety Considerations" on page 27.

7.2.2 Medical Tests and Other Devices

Call your doctor *before* you:

- have **any medical tests** that might affect, or be affected by, the VNS Therapy System (e.g., magnetic resonance imaging (MRI) scans).
- **you have an MRI scan.** Because you have a VNS Therapy System, you can have certain types of MRI scans but not others. If you have a MRI scan, it must be done under specific

conditions. **Call your doctor before you have an MRI scan.** See “Magnetic Resonance Imaging Warnings” on page 10.

- you have **any other medical devices implanted.**



Note: See “Medical Hazards” on page 11.

8 VNS Therapy Magnets

After your operation, your doctor will give you two magnets and accessories. Both styles of magnets contain a high-power magnet that is surrounded by a plastic casing in the shape of a watch. With normal use, they should remain powerful for approximately 3 years.

8.1 Magnet Cautions

- **If stimulation hurts,** contact your doctor right away
- **Always carry the magnet with you.** Show your family members or caregivers how to use it.
- **Do not place the magnet over a pacemaker** since it may affect pacemaker function and could change the pacing rate.
- **Do not place the magnet over a defibrillator** (sometimes called ICD) since it could turn the device OFF

8.2 Magnet Precautions

- **Never put or store the magnets near credit cards,** televisions, computers, computer disks, microwave ovens, watches, other magnets or items affected by strong magnetic fields. Keep them at least 25 centimeters (10 inches) away.
- **Do not drop the magnets.** They can break and lose magnetic strength if dropped on a hard surface.
- **To avoid cracking or damage to the plastic case,** The magnet should be stored at temperatures ranging from - 20 °C (- 4 °F) to + 55 °C (+ 131 °F).
- **If you lose one of your magnets and need a replacement,** contact your doctor.
- **If you are not sure how to use the magnet or have questions,** ask your doctor to show you how.

8.3 How to Handle the VNS Therapy Magnets

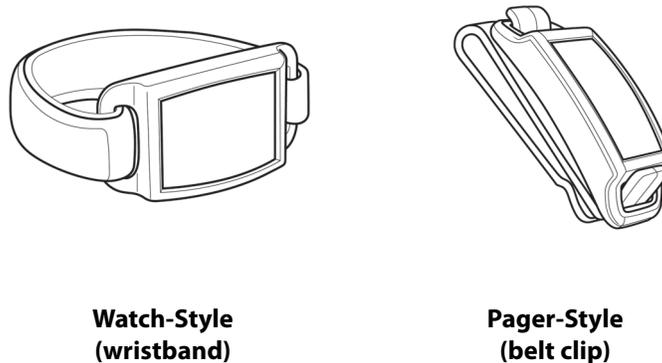
Your patient magnet will be given to you after your surgery. You should always carry the magnet with you. You can use the watch-style wrist band or belt clip, or keep the magnet in a pocket or purse. See “Magnet Accessories” on page 16 for more information. Follow all cautions listed above. The magnet can be cleaned with a soft cloth or sponge, and non-abrasive cleaner.

8.4 Magnet Accessories

The watch-style accessory attaches the magnet to your wrist with a wristband. The magnet should be on the inside of your wrist so it can be placed over the generator to stop stimulation.

The pager-style accessory holds the magnet in a belt clip like a pager. The magnet and clip can be removed without coming apart and placed against the generator to stop stimulation.

Figure 5. Magnet Accessories



**Watch-Style
(wristband)**

**Pager-Style
(belt clip)**

8.5 How the Magnet Works

VNS Therapy generators contain a component called a reed switch that can sense the presence of a magnetic field. When you pass or hold a magnet over the generator, the **reed switch** inside the generator closes like a gate. When the magnet closes it, the Normal signal (stimulation) cannot pass. While the magnet closes the switch, the generator is temporarily turned OFF. When the magnet is removed generator is turned back ON and can stimulate again.

8.6 How to Use the Magnet

Keep a magnet with you at all times in case you need to turn OFF the generator.

The magnet can be used to stop stimulation temporarily or turn OFF the generator when:

- you plan to sing or speak in public (if stimulation bothers you when you do this)
- 0
- you are eating (if you have swallowing problems)
- stimulation becomes uncomfortable or painful



The correct position for the magnet may vary from patient to patient. The position depends on how the generator is implanted. Find the position that works best for you.

8.6.1 To Stop Stimulation

1. Put the magnet over the generator (see Figure 6). If the stimulation stays on, move the magnet around until it stops.



Note: To show the correct position of the magnet with the generator, the magnet has been drawn without the belt clip or wristband. The belt clip and wristband use the same magnet.

Figure 6. Stop Stimulation



2. Leave the magnet over the generator. If needed, tape it to your chest or use an elastic, wrap-around bandage.
3. If you stopped the stimulation because it was painful or felt unusual, call your doctor right away.

With your doctor's permission, it is okay to leave the magnet in place for a short while, for example, to sing a song. The generator will not stimulate while the magnet is in place. The stimulation cycle begins again when the magnet is removed. Use the magnet only when necessary to turn off stimulation.

8.7 How to Replace the VNS Therapy Magnets

To order a new magnet, contact your doctor.



All magnets can **lose their effectiveness** over time. If you suspect that either of your magnets is not working, call your doctor.

9 Device Complications

Complications linked to the VNS Therapy System can result from:

- Surgery
- Generator malfunction (not working)
- Battery depletion (running out)
- Touching or moving the device through the skin

9.1 Surgery

All types of surgery carry some risks. In addition to the risks described in “Side Effect and Safety Profile of VNS Therapy Observed in Clinical Studies in Depressed Patients” on page 24, there are potential mechanical complications related to the surgical implantation of the device. The generator and/or lead can—but rarely do—move or come through the skin. Also, the lead can break or become disconnected from the generator.

9.2 Generator Malfunction (Device Not Working Right)

The generator can malfunction, though this is rare. The stimulation from a generator that is not working right can cause intense neck pain, hoarseness, choking, or trouble breathing.



Stimulation from a generator that is not working right could damage the vagus nerve and lead to permanent hoarseness or other complications. Malfunction of the generator could cause the battery to run out sooner than expected. **If you have any of these symptoms**, or if stimulation becomes painful, irregular, or nonstop, place the magnet over the generator hold it there to stop stimulation (see “How to Use the Magnet” on page 16), and **call your doctor right away**.

9.3 Battery Depletion (Running Out)

The battery in the generator can last from 1 to 16 years. The lifespan depends on these factors:

- Generator model
- Stimulation settings your doctor chooses
- Interaction of the lead and vagus nerve over time

The generator battery will slowly lose its power. When it starts to run out, it will begin to stimulate differently. You may sense this change as irregular stimulation. At the end of battery life, the stimulation will stop completely.

The dose settings impact how long the battery in the generator will last. For example, the battery may last for 3 years at a higher setting, compared with 8 years at a lower setting. For the full range of settings in relationship to battery life, ask your doctor.

When the battery in your generator runs out, the generator must be replaced in order for you to continue to receive VNS Therapy. This requires an additional surgical procedure. The operation involves anesthesia and generally takes less than an hour to complete.

Replacement or removal of the lead is a different procedure. It is not required for routine replacement of the generator.



After stimulation stops completely (e.g., the generator battery runs out), you may notice a change in your depressive symptoms. If you think the generator might not be working right, call your doctor.

9.4 Manipulation of the Generator and Lead

The generator is secured into place during surgery, but the device can move slightly. It may be possible to feel the lead under the skin after surgery. This feeling is normal and should become less obvious over several weeks. Manipulation of the lead should be prevented at all times.



Never move or twist the generator or manipulate the lead. Doing so could damage the lead or your vagus nerve. It could require that the generator and lead be replaced.

10 Patient Warranty and Safety Listing

Government agencies require makers of implantable devices to contact people in case of emergencies related to the device. LivaNova has a list of people who have had the generator and lead implanted. The information is kept in confidential files. It is a permanent record of the implantation surgery. LivaNova will release a file only if required by law.



Send LivaNova **a change of address notice if you move**.

11 **Frequently Asked Questions**

How do most people respond to VNS Therapy?

When the device was tested in the clinical trials, depressive symptoms decreased for most patients. Some patients had no change in depressive symptoms and some got worse while receiving VNS Therapy. Among those patients who did improve while receiving VNS Therapy, some did not improve until they had been receiving VNS Therapy for 6 months or longer.

Can I know if I will be helped before I am implanted with the generator and lead?

At this time, there is no way to predict what your response will be.

What are the results of the VNS Therapy clinical studies?

This Manual provides a summary of important safety and effectiveness results from the clinical studies. Your doctor can give you more information about the clinical (research) studies.

What are the side effects of VNS Therapy?

The most common side effects reported during VNS Therapy are voice alteration (often described as hoarseness), discomfort in the neck (typically mild pain or a tingling sensation), cough, shortness of breath, difficulty swallowing, and a feeling of tightness in the throat. Often these events only occur when the generator is ON. Other less common side effects are discussed in "Side Effect and Safety Profile of VNS Therapy Observed in Clinical Studies in Depressed Patients" on page 24. In general, most side effects become less noticeable over time.

What is the implantation surgery like?

You will be given a general or local anesthetic. The operation usually takes 1 to 2 hours. The operation will be done with you as an outpatient (you go home the same day) or you may stay in the hospital overnight. Ask your surgeon to tell you more about the anesthetic, the operation, and the hospital stay so that you will know what to expect.

Are there risks linked with the surgery?

Any surgery has some type of risk. It is important that you discuss this question with your surgeon.

Will the scars be noticeable?

Each person has different healing and scarring results. You should expect some scarring from surgery. Most people do not think the scarring after surgery is a major concern. If this is a special concern for you, discuss it with your surgeon.

Will people be able to see the implanted device through my skin?

The generator is shaped like a disk. If you have a small frame or are very thin, the device may be visible below your left collarbone.

- Model 101 — 5.4 centimeters (2.1 inches) across and 1 centimeter (0.4 inch) thick; it weighs about 38 grams (1.34 ounces).

- Model 102 — 5.2 centimeters (2.0 inches) across and 0.7 centimeter (0.27 inch) thick; it weighs about 25 grams (0.88 ounce).
- Model 102R — 5.2 centimeters (2.0 inches) by 5.8 centimeters (2.3 inches) and 0.7 centimeter (0.27 inch) thick; it weighs about 27 grams (0.95 ounce).
- Model 103 — 4.6 centimeters (1.8 inches) by 3.3 centimeters (1.3 inches); it weighs about 16 grams (0.56 ounce).
- Model 104 — 4.6 centimeters (1.8 inches) by 4.1 centimeters (1.6 inches); it weighs about 18 grams (0.63 ounce).
- Model 105 and 106 — 5.2 centimeters (2.0 inches) across and 0.7 centimeter (0.27 inch) thick; it weighs about 25 grams (0.88 ounce).
- ◆ Model 1000 — 4.5 centimeters (1.77 inches) by 3.2 centimeters (1.26 inches) and 0.69 centimeters (0.27 inches) thick; it weighs about 16 grams (0.56 ounce)

What happens after the surgery?

After surgery (usually 2 weeks later), your doctor will program the treatment settings of your device. If the stimulation feels uncomfortable, your doctor can change it to make you more comfortable. The doctor will use the programming wand to check and fine-tune your stimulation settings at subsequent visits.

Will I be able to tell when the stimulator is on?

Many people note a change in their voice (often described as hoarseness) or discomfort in the neck (typically mild pain or a tingling sensation) during stimulation. In general, most side effects become less noticeable over time.

What does the magnet do?

The magnet is used to stop stimulation.

When should I use the magnet?

Use the magnet to stop stimulation temporarily or to turn OFF the generator when you plan to sing or speak in public (if stimulation bothers you when you do this), when you are eating (if you have swallowing problems), or if stimulation becomes uncomfortable or painful. If you need to use the magnet for any of these reasons or any other reason, inform your physician.

Is it possible to stop all stimulation using the magnet?

Yes. To stop stimulation, hold the magnet over the generator and keep it there. Use this method if you have unusual or painful stimulation. Then call your doctor right away. The magnet will stop all stimulation while it is held in place. You may need to secure the magnet by taping it over the implanted device.

What if the magnet is accidentally kept in place over the generator for an extended period?

No stimulation will be delivered while the magnet is kept over the generator. Stimulation will resume only after the magnet is removed.

How does the magnet work?

The generator has a sensor (the reed switch) that recognizes the magnet and stops stimulation.

Can any magnet be used?

Only the VNS Therapy magnet should be used with your VNS Therapy System. If you lose your magnet or need extra magnets, contact your doctor. In an emergency, you may try other strong magnets. The use of other magnets will not harm the VNS Therapy System, but there is no way to know in advance whether a magnet other than the VNS Therapy magnet will work.

Who should carry the magnet?

You should carry the magnet with you at all times. You may also want your family members or caregivers to carry a VNS Therapy magnet.

Is the magnet an environmental hazard?

The VNS Therapy magnet can damage computer disks, credit cards, watches, and other items affected by strong magnetic fields. Keep your magnet at least 25 centimeters (10 inches) away from any of these items. Do not store magnets near such items.

Will dropping my magnet affect its strength?

Dropping your magnet should not affect the magnet's strength. This is a common problem with low-power magnets. The VNS Therapy magnet is a high-power magnet and should not lose its strength when dropped or if the casing cracks.

How long will my magnet last (does it have an expiration date)?

Based on normal use, the VNS Therapy magnet should have an approximate service life of 3 years.

Questions?

If you have other questions about the VNS Therapy System, any of its parts, or VNS Therapy in general, talk to your doctor.

12 Glossary

adjunctive therapy

Additional, add-on; VNS is adjunctive therapy, that is added on to other antidepressant treatments

aspiration

Accidental sucking in of food particles or fluids into the lungs

clinical benefit

Categories assigned to describe change in depressive symptoms on Hamilton Rating Scale for Depression-24 Item after VNS Therapy

- meaningful clinical benefit – 25% to 49% improvement in depressive symptoms

- highly meaningful clinical benefit – 50% to 74% improvement in depressive symptoms
- extraordinary clinical benefit – over 75% improvement in depressive symptoms

clinical studies

Tests of the effectiveness and safety of a therapy on humans

diathermy

Diathermy is a treatment to promote healing or relieve pain

dysautonomia

A term used to describe several different medical conditions that cause a malfunction of the Autonomic Nervous System, which controls the “automatic” functions of the body that we don’t consciously think about (e.g., heart rate, blood pressure, digestion, dilation, and pupil constriction, kidney function and temperature control)

electrode

Part of the VNS Therapy lead that connects to the vagus nerve

HRSD₂₄

Standardized test to measure depressive symptoms as reported by the doctor; Hamilton Rating Scale for Depression-24 Item

IDS-SR₃₀

Standardized test to measure depressive symptoms as reported by the patient, Inventory of Depressive Symptomatology Self-Report

lead

VNS Therapy lead; small wire that connects the VNS Therapy generator to the vagus nerve

LivaNova

Company that makes the VNS Therapy System

MADRS

Standardized test to measure depressive symptoms as reported by the doctor, Montgomery-Asberg Depression Rating Scale; commonly used in Europe

MR

Magnetic resonance

MR Conditional

An item that has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use

MR Unsafe

An item that poses hazards in all MRI environments

MRI

Magnetic resonance imaging

programming wand

VNS Therapy instrument used to check or change VNS Therapy device and settings

generator

VNS Therapy device implanted in the patient's chest; holds the battery and delivers stimulation to the vagus nerve through the VNS Therapy lead

reed switch

A mechanism that works like a gate. When the magnet closes it, the signal (stimulation) cannot pass; the generator is temporarily turned OFF

remitter

Study participant who was essentially free of depressive symptoms after receiving VNS Therapy; determined by scores of standardized tests; also called complete responder

responder

Study participant whose depressive symptoms were reduced by 50% or more after receiving VNS Therapy; determined by scores of standardized tests

stimulate

Send electrical signal; with VNS Therapy, the generator sends an electrical signal through the lead to the vagus nerve, which carries the signal to the brain

stimulation

The electrical signal that is sent from the generator to the brain

treatment-resistant depression (TRD)

Depression that has not responded to four or more antidepressant treatments

vagus nerve

A nerve that extends from the brain through the neck to the major organs (e.g., heart, lungs, and stomach, etc.) in the torso

vagus nerve stimulation (VNS)

Periodic electrical signals sent from the generator to the vagus nerve

VNS Therapy[®]

Treatment received from vagus nerve stimulation

VNS Therapy System

All of the parts that provide VNS Therapy: generator, lead, programming wand, programming computer, programming software, and magnets

13 Contact Information

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14 Appendices

14.1 Side Effect and Safety Profile of VNS Therapy Observed in Clinical Studies in Depressed Patients

This section describes the side effects and safety concerns that were observed in the clinical studies that led to the approval of VNS Therapy as a treatment for patients with treatment-resistant depression. The side effects and safety concerns associated both with the surgical implantation procedure for the VNS Therapy System and those related to stimulation of the vagus nerve are discussed. In addition, this section discusses some specific safety considerations for the treatment of patients with depression.

14.1.1 Overview of Clinical Studies

Safety and effectiveness studies involved a total of 295 men and women who received VNS Therapy along with their usual antidepressant treatments. Sixty of them participated in a pilot study that compared depressive symptoms before and after VNS Therapy. The favorable results from that study prompted a second study. The second study (sometimes referred to as "D-02") consisted of two "phases" and included people with treatment-resistant depression. In the first phase, which lasted 3 months, half of the 235 patients who were implanted with the device had it turned on while the other half did not. Patients did not know whether the device was on or not. In the second phase of the study (referred to as the "long-term phase of D-02"), all patients had the device turned on after the first 3 months and were followed for at least a full year. Patients in the long-term phase of the study were allowed to have adjustments in the doses of depression medications prescribed and were also allowed to have new medications or ECT prescribed during this time. These patients were compared to a separate group of 124 people with treatment resistant depression who received antidepressant treatments, but who did not have the device implanted.

14.1.2 Surgical Implantation Procedure

14.1.2.1 Side effects that may occur from implantation of the VNS Therapy System

The following is a list of the side effects that were most commonly reported as being related to the surgical implantation of the VNS Therapy System during the D-02 study. The side effects that occurred in at least 3% of the patients in the D-02 study and the percentage of patients who experienced them were as follows:

- Incision pain (36%)

- Voice alteration (33%)
- Incision site reaction (for example, redness, itching, soreness) (29%)
- Pain around the device generator or leads (23%)
- Other reactions around the device generator or leads (for example, swelling, tenderness) (14%)
- Pharyngitis (inflammation of the throat) (13%)
- Difficulty swallowing (11%)
- Numbness (11%)
- Nausea (9%)
- Shortness of breath (9%)
- Headache (8%)
- Neck pain (7%)
- Pain elsewhere (7%)
- Increased cough (6%)
- Paresthesia (tingling sensation) (6%)
- Infection at the surgical site (4%)
- Chest pain (3%)
- Dizziness (3%)
- Increased tension of the muscles (3%)
- Vocal cord paralysis (3%)
- Skin rash (3%)
- Inability to pass urine (urinary retention) (3%)

Many of these side effects resolved within 30 days, but in some cases the side effects persisted beyond 90 days. Voice alteration was particularly likely to persist for longer than 90 days.

14.1.2.2 Infrequent surgical side effects

Surgical side effects that were reported in the D-02 study less frequently than those listed above, but by at least 1% of patients, were as follows: allergic reactions, weakness, fever, bleeding, heart palpitations, difficulty sleeping, neck rigidity, loss of appetite, heartburn, vomiting, bruising, swelling, itching, ear pain, ringing in the ears, and tightness in the throat. Additional serious side effects (reported in less than 1% of patients) were: transient heart stoppage (occurred in the operating room), decrease in heart rate (occurred in the recovery room), abnormal thinking (occurred in the post-operative period, thought due to narcotics), aspiration pneumonia (occurred in the post-operative period), and acute kidney failure.

 Implantation of the lead may cause nerve constriction (squeezing of the nerve). Call your doctor right away if your voice is always hoarse a few days after surgery. (There could be other explanations for this symptom.)

 If you undergo VNS generator replacement with a larger size device, you may initially experience increased discomfort or inflammation at the surgery site. Call your doctor if you experience symptoms that are concerning or do not improve.

14.1.2.3 **Surgical scars**

There are surgical techniques that may minimize surgical scars. Talk to your surgeon if you have specific concerns.

14.1.3 **Stimulation of the Vagus Nerve**

Side effects can occur from stimulation of the vagus nerve by the VNS Therapy System. Generally, the side effects become less noticeable over time for most patients. Only 3% of patients discontinued VNS Therapy because of side effects during the first year of treatment in the D-02 study. Sometimes your doctor can lessen the side effects by changing the device settings.

The VNS Therapy System is not a drug. It does not cause drug-related side effects and does not interact with drugs, including antidepressant medications you may be taking.

14.1.3.1 **Side effects that may occur from stimulation of the vagus nerve**

Table 2 shows the side effects that were most commonly reported as being related to stimulation of the vagus nerve by the VNS Therapy System during the D-02 study. Side effects reported in at least 3% of the patients are included. Table 2 shows the percentage of patients who had these side effects after 3 months, 12 months, and 24 months of stimulation.

Table 2. Stimulation-Related Side Effects Reported by Greater Than or Equal To 3% of Patients—Study D-02

	Months of Stimulation		
	3	12	24
Voice alteration	59%	54%	52%
Increased cough	24%	7%	4%
Shortness of breath	14%	16%	14%
Neck pain	16%	13%	15%
Difficulty swallowing	13%	5%	5%
Paresthesia (tingling)	11%	4%	4%
Tightness in throat	10%	6%	5%
Pain	6%	6%	5%
Nausea	6%	1%	1%
Pharyngitis (inflammation of the throat)	6%	5%	4%
Headache	5%	3%	3%
Chest pain	4%	2%	2%

	Months of Stimulation		
	3	12	24
Heart palpitations	4%	3%	2%
Difficulty sleeping	4%	1%	1%
Heartburn	3%	2%	2%
Increased muscle tension	3%	4%	3%

While many of the incidences of these side effects resolved over time, some patients continued to report the side effects throughout the study. This was particularly true for voice alteration, shortness of breath, and neck pain. Some of the side effects caused by stimulation typically occur only during stimulation (the ON time of the stimulation cycle).

14.1.3.2 **Other side effects reported during VNS Therapy**

The following is an alphabetical list of additional side effects reported as at least possibly due to vagus nerve stimulation during the 12-month D-02 study: abnormal dreams, abnormal thinking, agitation, amenorrhea (stoppage of menstrual periods), amblyopia (visual disturbance), amnesia, anxiety, arthralgia (joint pain), asthma, colitis, constipation, deafness, diarrhea, dry mouth, emotional lability, eructation (belching), eye pain, flatulence, flu syndrome/viral infection, gastritis, hiccup, hypertension (high blood pressure), hypotension (low blood pressure), increased appetite, laryngitis, migraine, myalgia (muscle ache), myasthenia (muscle weakness), nervousness, postural hypotension (low blood pressure upon standing), rhinitis, sedation, stridor, sweating, syncope (fainting), tachycardia (fast heart beat), tremor, twitching, vasodilatation (flushing), weight gain, weight loss.

14.1.4 **Additional Safety Considerations**

14.1.4.1 **Worsening depression**

People who have depression can experience waxing and waning of their depressive symptoms even while receiving treatment. During the first phase of the D-02 study when half the patients had their VNS Therapy System turned on and the other half did not, the study doctors reported 12 serious events of worsening depression that required hospitalization. Four of these events occurred in patients who had their device turned on, and the other eight occurred in patients who did not have their device turned on. During the long-term phase of the D-02 study (months 3 through 12), study doctors reported 62 additional serious events of worsening depression in 31 patients. If your depression worsens during VNS Therapy, inform your doctor promptly.

14.1.4.2 **Mania**

Some patients being treated for depression may experience a manic or hypomanic episode characterized by an abnormal and persistently elevated or irritable mood. Patients with known bipolar disorder (manic depressive illness) are the people most likely to experience this phenomenon. It is believed that effective antidepressant treatments themselves can cause a manic or hypomanic episode. In the D-02 study (through the 12-month long-term phase), six hypomanic or manic episodes were observed. Five of the six patients had a known history of prior hypomanic or manic episodes. One of these events was considered serious enough to require hospitalization; the other five events were either treated with medication or only required

observation. If you experience symptoms of an elevated or irritable mood during VNS Therapy, inform your doctor promptly.

14.1.4.3 **Suicides**

People with depression may experience the emergence of suicidal thoughts and behavior (suicidality) whether or not they are receiving treatment. In the D-02 study (through the 12-month long-term phase), there were one suicide and seven additional suicide attempts in six patients. If you or someone else notices your depression worsening or indications of suicidality, inform your doctor promptly. Additionally, if you or someone else notices any of the following symptoms, inform your doctor immediately as they may indicate an increased risk of suicide: new or worse anxiety, feeling agitated or restless, panic attacks, difficulty sleeping, new or worse irritability, acting aggressive, being angry or violent, acting on dangerous impulses, an extreme increase in activity and talking, other unusual changes in behavior or mood.

14.1.4.4 **Deaths that occurred during the depression studies**

In the D-02 study (through the 12-month long-term phase), there were four deaths. One occurred in a patient who had enrolled in the study but had not yet received a VNS Therapy System implant. The causes of death for the other three patients were as follows: suicide (described above), sudden death of unknown cause, multi-organ system failure.

14.1.5 **Analysis of Medical Device Reports Submitted to FDA from July 1, 1997 through October 8, 2004 for the VNS Therapy System Epilepsy Indication**

Once a medical device is approved for commercial distribution, the United States Food and Drug Administration (FDA) regulations require certain parties, including manufacturers of medical devices, to report to the FDA deaths and serious injuries to which a device has or may have caused or contributed. The required report is referred to as a medical device report (MDR). The FDA Office of Biometrics and Surveillance analyzed all MDRs submitted for the VNS Therapy System from July 1, 1997 through October 8, 2004. During this period, the VNS Therapy System had a single approved indication, epilepsy. The analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. By the end of the period analyzed, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience (the presence of the implanted device in an individual for a full year equals one "device-year"). **It is important to emphasize that, although the events occurred during treatment with the VNS Therapy System, the submission of an MDR does not necessarily mean the product caused or contributed to the event being reported.**

14.1.5.1 **Deaths**

A total of 524 deaths were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Of the 524 deaths, 102 (20%) were of an "unknown cause," including 24 deaths of unknown cause that occurred during sleep (5% of total deaths). Of those deaths with a reported cause, the following were the most common etiologies:

- Seizure disorder (152 reports; 29% of total deaths), including sudden unexplained death in epilepsy and status epilepticus (These are recognized risks in patients with epilepsy—the rate of sudden unexplained death in patients treated with VNS Therapy is within the range of the rates reported for similar patients who are treated with antiepileptic drugs without VNS Therapy.)

- Respiratory events (99 reports; 19% of total deaths), including pneumonia, pulmonary edema, reduced oxygen supply to body tissues
- Cardiac events (51 reports; 10% of total deaths), including heart stoppage, heart attack, and irregular heart beat
- Neurovascular events (24 reports; 5% of total deaths), including stroke and brain hemorrhage (bleeding)
- Cancer (19 reports; 3% of total deaths), including brain and colon
- Suicide (9 reports; 2% of total deaths)

14.1.5.2 Serious injuries

A total of 1,644 serious injuries were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. The most frequently reported serious injury was infection (525 reports). Approximately 40% of these were known to have required device removal. The second most common serious injury reported was increased seizure activity (324 reports). Others included:

- Vagus nerve injury (181 reports) including vocal cord paralysis (109) and hoarseness (71)
- Respiratory injuries (141 reports) including sleep apnea (cessation of breathing during sleep, 33 reports) shortness of breath (50), and aspiration (inhaling foreign matter or stomach contents into the lungs, 14 reports)
- Cardiac events (123 reports) including fast or slow heart rates, palpitations, high or low blood pressure, fainting, and cessation of heart beat
- Pain (81 reports) including chest and neck pain
- Gastrointestinal events (60 reports) including difficulty swallowing (24) and weight loss (24)
- Depression (21 reports)

Of the 1,644 reports of serious injury, 694 (42%) were associated with subsequent device removal in that subject.

14.1.5.3 Device malfunctions

A total of 708 device malfunctions were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Some of the most common malfunctions reported were an abnormal lead test (which can be indicative of a poor connection between the lead and vagus nerve or lead and generator or can indicate a broken lead, 351 reports), lead breakage (116), device failure (44), and a shift in device location (20).

