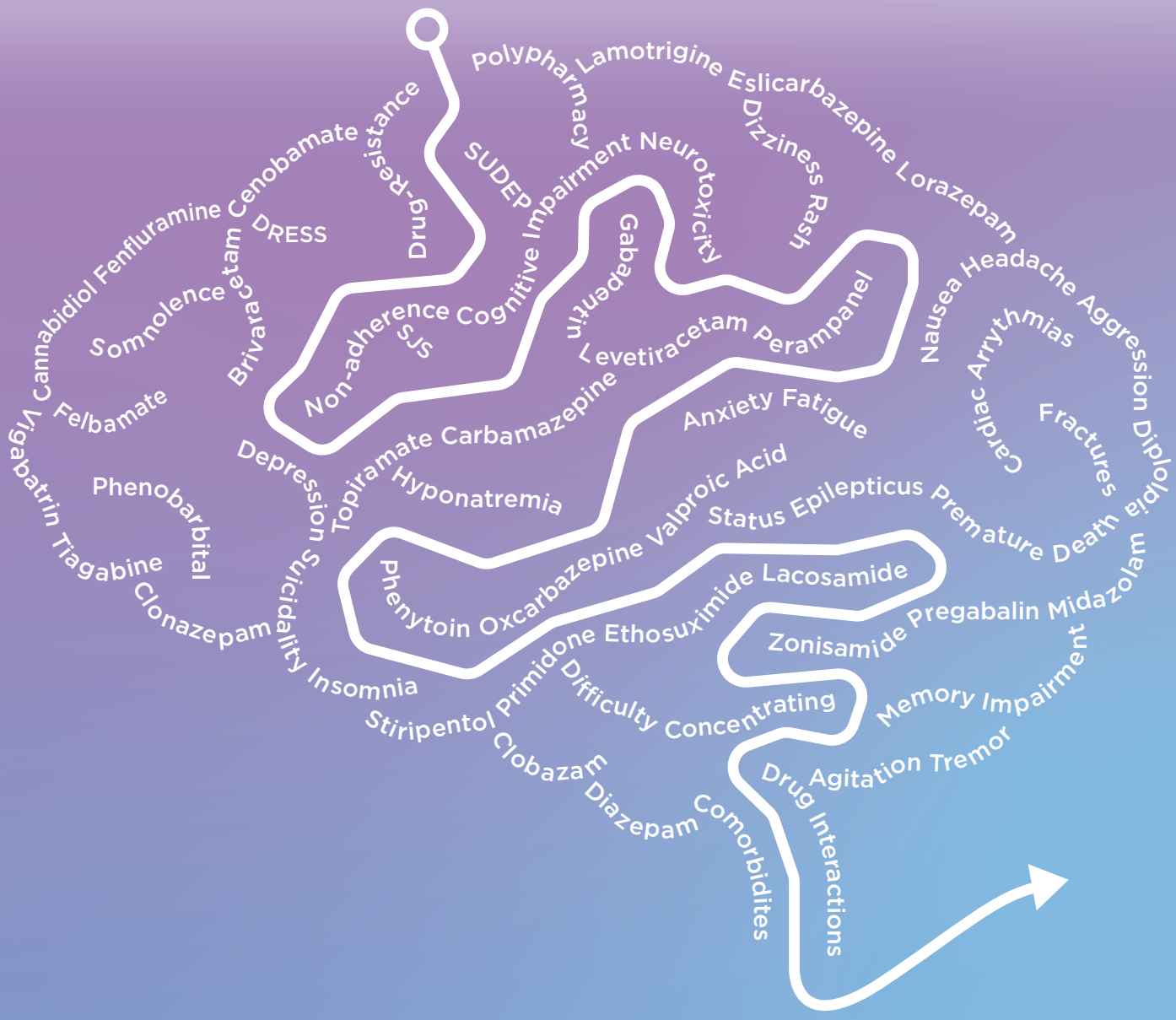
25 YEARS OF VNS THERAPY®

Helping patients drugs still haven't, in ways drugs still can't.

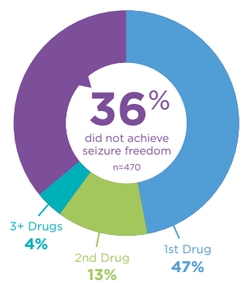


VNSTherapy® | LivaNova

25 YEARS OF VNS THERAPY

Helping patients drugs still haven't, in ways drugs still can't.

1984-1997: LIKELIHOOD OF ACHIEVING **SEIZURE FREEDOM**[1] with anti-seizure medications (ASMs)

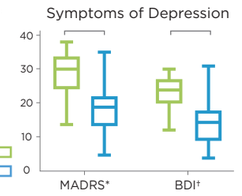


Minimum 1 year of seizure freedom on unchanged treatment regimen

VNS Therapy significantly reduces symptoms of comorbid depressive disorders in DRE patients[15]

Improvement after one year of VNS Therapy for patients with DRE and comorbid depressive disorders[15] (n=59)

Reduction in **MADRS** score from 29 to 18 and **BDI** from 24 to 14 overall (p<0.001)



*Montgomery-Asberg Depression Rating Scale
†Beck Depression Inventory

Comorbid depressive and anxiety disorders are a persistent unmet need in epilepsy treatment[8,11]

30-55% of DRE patients have **depressive disorders**[9-12]

Comorbid depression and anxiety disorders **decrease tolerability** of ASMs and **increase nonadherence**[9,10,13]

Patients with comorbid depression are **23x more likely** to die of **suicide** than the general population[14]

1999-2003: MOOD, MEDICATIONS & EPILEPSY

"Between keeping track of appointments and medications, not having anyone I felt safe confiding in, and normal teen angst, my self-esteem and self-worth were destroyed. I struggled to make friends. **While everyone else was living their lives, I withdrew further into myself.**"

VNS Therapy supports adjunctive treatment with no drug interactions or CNS side effects[23]

Most common adverse events occur during stimulation and generally diminish over time[23,24]

Side Effect	Year 1	Year 2	Year 3
Hoarseness	29%	19%	2%
Paresthesia	12%	4%	0%
Cough	8%	6%	2%
Shortness of Breath	8%	3%	3%

Frequent adverse effects and potential drug interactions limit safety, tolerability of ASMs[21]

20% of ASMs are discontinued within 6 months due to AEs, often at low doses[20]

Polypharmacy increases risk for adverse **systemic and neurotoxic** effects of ASMs[20,21]

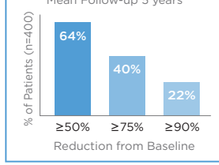
ASM toxicity can lead to increased **anxiety**, **sleep problems**, and **daytime sleepiness**[22]

2007: WILLIAM RECEIVES VNS THERAPY, age 20 years

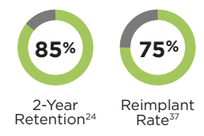
"During a routine visit, my neurologist told me about a different treatment method. Since **medication alone could not control my seizures**, he said VNS Therapy might help. Though there were potential side effects, to me **the potential benefits outweighed the risks**."

VNS Therapy provides long-term seizure control with proven safety, tolerability[23,24]

Long-Term Seizure Control[36]
Mean Follow-up 5 years



Long-Term Retention with VNS Therapy



For most DRE patients, new drug therapies alone will not be enough to control seizures

long-term retention for most ASMs is **35-70%** at 2 years and 30-60% at 3 years[34,35]

<10% of DRE patients achieve **seizure freedom** and **<40%** achieve seizure reduction ≥50% with a newly introduced ASM[30,31]

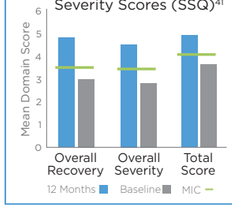
3/4 of patients who achieve remission ≥12 months on a new ASM will **relapse within 5 years**[32,33]

2012: WILLIAM CHOOSES TO REIMPLANT

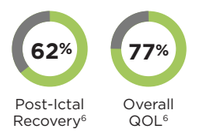
"Because **VNS Therapy made such a difference in my day-to-day life**, I had the generator replaced when the battery started running out. Like the first time, it was an out-patient procedure, and the new one works just fine."

VNS Therapy leads to fewer, shorter, less severe seizures and significant improvements in QOL[6,40,41]

Improvements in Seizure Severity Scores (SSQ)[41]



Patients Rated Improved Post-Implant



Maximum achieved during follow-up period 24-48 months (N=1194)

Success in DRE treatment is defined by more than just reductions in seizure frequency

Seizure severity contributes to **seizure worry** and impaired **cognition** and **social functioning**[38,39]

Depression and **ASM toxicity** are the strongest and most consistent **negative predictors for QOL** in DRE[4,8,10,11]

2015-2018: CREATING A NEW FUTURE

"Today, the future looks promising. Thanks to VNS Therapy, **I have better control over my seizures** than I did before, and a **much better outlook on life**. I have earned my Bachelor's degree, and now I'm working on additional certifications."

First Patient implanted with VNS Therapy — 1988

Individual patient experience. Results may vary.

FDA Approval Granted for Drug Resistant Epilepsy

Model 100 Pioneering Device Solution for Epilepsy — 1997 — 1,200 Patients Implanted

Model 101 Smaller Device Improved Battery Life — 2000 — 11,000 Patients Implanted

Pulse™ 102 Increased Comfort Faster Programming — 2002 — 21,000 Patients Implanted

FDA Approval for **Treatment Resistant Depression** — 2005 — 37,000 Patients Implanted

Demipulse® 103 Smallest & Lightest Device — 2007 — 47,000 Patients Implanted

AspireHC® High Capacity Battery Longer Device Lifespan — 2011 — 65,000 Patients Implanted

AspireSR® First Responsive VNS Therapy Device — 2015 — 88,000 Patients Implanted

SenTiva® Smallest & Lightest Responsive Device for DRE — 2017 — 120,000+ Patients implanted with VNS Therapy — 2020

1998: WILLIAM DIAGNOSED WITH EPILEPSY, age 12 years

"Life following my diagnosis was **chaotic and difficult**. Though my parents researched focal epilepsy, they still seemed uncertain about how to handle it. They became a little **overprotective** and **worried about my seizures**. My peers didn't seem to try to understand. I once had a seizure in class, and everyone was somewhat awe-struck and dumb-founded. After that, **I did my best to hide it**."

2000-2005: WHAT HAPPENS WHEN DRUGS FAIL?

"I kept trying to find the right treatment, or combination of treatments, to help control my epilepsy. After taking **at least 12 different medications**, I had my first brain surgery. There were no complications, but the surgery didn't help control my seizures. After a second surgery failed, **I felt I had no choice but to take different medications and hope for the best.**"

2008-2012: THE VNS THERAPY ADVANTAGE

"At first, I was still having seizures. But after trying different settings, we found what works for me. Now, **along with taking my medication, I am finally able to control my seizures**. Occasionally, I might have an aura or a breakthrough seizure, but those are **few and far between**."

Epilepsy and drug therapies can both have negative psychosocial and cognitive impacts[2,3]

63% of patients report feeling epilepsy-related **stigma,** which is associated with increased **seizure worry** and **impaired quality of life**[4,5]

>65% of patients report cognitive impairment such as **memory loss** and **difficulty thinking**[2]

Consequences of not pursuing further treatment of DRE include increased risk of morbidity and mortality

DRE patients are **2x** more likely to be **hospitalized** or visit the **emergency department**[16]

up to 13.4x greater risk of **premature death** in patients with poorly controlled epilepsy, compared to seizure free patients[17]

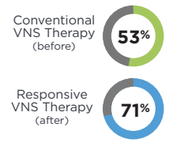
Managing DRE effectively requires minimizing side effects, maximizing adherence and QOL[25]

85% of DRE patients are **willing to change to a new treatment** that might maintain current level of seizure control but **without ASM side effects**[2]

approx. 1 in 3 epilepsy patients are **not adherent** to their ASMs, which **increases risk** for poor outcomes[13,26]

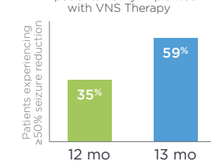
Responsive VNS Therapy provides enhanced seizure control and earlier onset of effect[42]

Improved Responder Rate with AutoStim[42]



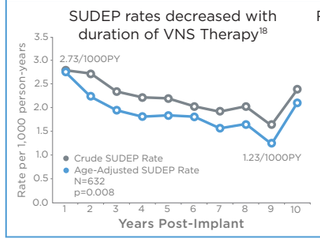
Patients with >50% reduction in seizure frequency after changing from conventional to responsive VNS Therapy (n=62)

Earlier Onset of Effect
in patients newly implanted with VNS Therapy



VNS Therapy reduces SUDEP, health-related events

SUDEP rates decreased with duration of VNS Therapy[18]

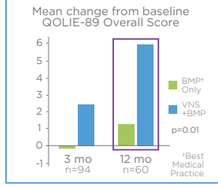


Reductions in Health-Related Events[19]

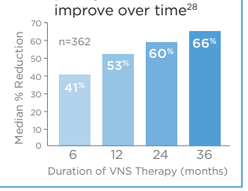
N=1,655
Avg follow-up 30.4 months Post-Implant

VNS Therapy offers maximum adherence, better QOL, seizure control that improves over time[27]

Better QOL with adjunctive VNS Therapy[29]
Mean change from baseline QOLIE-89 Overall Score

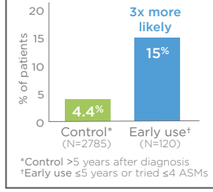


Early reductions in seizure frequency that continue to improve over time[28]



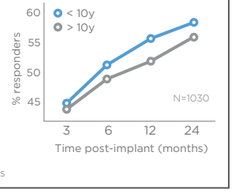
Earlier use of VNS Therapy is shown to lead to better outcomes

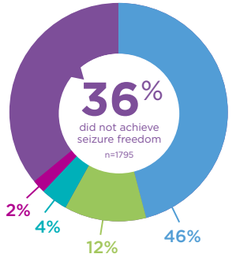
Early Use cohort more likely to be seizure free 3 months post-implant[44]



*Control >5 years after diagnosis
†Early use ≤5 years or tried ≤4 ASMs

Patients with duration <10 years of seizures responded better[45]





1984-2014: LIKELIHOOD OF ACHIEVING **SEIZURE FREEDOM** with anti-seizure medications (ASMs)

ASM Regimens Trialed
1st 2nd 3rd 4+

Over the last 30 years, despite the addition of more than 12 new ASMs: Seizure freedom rates in newly diagnosed epilepsy have not improved. Rates of withdrawal due to nervous system and psychiatric AEs have significantly increased. And overall tolerability rates **have not improved**.[20,46]

WHY WAIT FOR ANOTHER DRUG TO FALL SHORT?

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INTENDED USE/INDICATIONS

The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications.

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.

Incidence of adverse events following stimulation (>5%) were voice alteration, increased coughing, pharyngitis, paresthesia, dyspnea, dyspepsia, and nausea.

See important safety information at **VNSTherapy.com**

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IM-7320000-EPI

Brief Summary[1] of Safety Information for the VNS Therapy® System [Epilepsy Indication] (September 2017)

1. Intended Use / Indications

Epilepsy (US)—The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications.

2. Contraindications

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

Diathermy—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 — 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 have not been established for uses outside the "Intended Use/Indications" section of the physician's manuals.

The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) 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 arrhythmias.

It is important to follow recommended implantation procedures and intraoperative product testing described in the *Implantation Procedure* chapter 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 a System Diagnostics (Lead Test) 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 and those with a history of drooling or hypersalivation are at greater risk for aspiration. Use of the magnet to temporarily stop stimulation while eating may mitigate the risk of aspiration.

Dyspnea (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 OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder.

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause 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 have MRI procedures performed only as described in the *MRI with the VNS Therapy System* instructions for use. In some cases, surgery will be required to remove the VNS Therapy System if a scan using a transmit RF body coil is needed.

Excessive stimulation at an excess duty cycle (that is, one that occurs when "ON" time is greater than "OFF" time) and high frequency stimulation (i.e., stimulation at ≥ 50 Hz) has resulted in degenerative nerve damage in laboratory animals.

Patients who manipulate the generator and lead through the skin (Twiddler's Syndrome) may damage or disconnect the lead from the generator and/or possibly cause damage to the vagus nerve.

Generators with AutoStim only—The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias currently being managed by devices or treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications). Patients also should not have a history of chronotropic incompetence [commonly seen in patients with sustained bradycardia (heart rate < 50 bpm)].

Generators with AutoStim only—For anticipated use of the AutoStim feature, it is important to follow the recommended pre-surgical surface assessment described in the Implantation Procedure to determine a location for the generator to reside in which it can accurately detect heart beats

4. Warnings — Epilepsy

The VNS Therapy System should only be prescribed and monitored 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 consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others.

Sudden unexpected death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexpected deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates.

5. Precautions — General

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy physician's manuals.

Prescribing physicians should be experienced in the diagnosis and treatment of 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 should be used during pregnancy only if clearly needed.

The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating 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 should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. Children 4-11 years of age may have a greater risk for infection when compared to adolescent and adult patients (≥ 12 years). Careful monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be stressed.

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, defibrillatory 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 to + connection) into the generator's lead receptacles.

The patient can use a neck brace for the first week to help ensure proper lead stabilization.

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.

For Models 100, 101, 102 and 102R do not use frequencies of 5 Hz or below for long-term stimulation.

Resetting the generator disables or turns the device OFF (output current = 0 mA). For Model 100, 101, 102 and 102R, resetting the generator will result in device history loss.

Patients who smoke may have an increased risk of laryngeal irritation.

Generators with AutoStim only—Because the device senses changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where the heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc. Adjustments to the AutoStim feature's detection threshold should be considered; which may include turning the feature OFF.

Generators with AutoStim only—The physical location of the device critically affects the feature's ability to properly sense heart beats. Care must be taken to follow the implant location selection process outlined in the Implantation Procedure.

Generators with AutoStim only—Talk to your patient about use of the AutoStim feature since use of the feature will result in faster battery drain and the potential for more frequent device replacements. The physician's manual describes the impacts to the battery life. The patient should return to their physician at appropriate intervals to further evaluate whether they are receiving benefit from the current AutoStim settings.

M1000 only — Since the Scheduled Programming feature allows the generator to apply therapy increases at scheduled intervals, it may not be appropriate for use in patients who are nonverbal or are unable to use the patient magnet to stop undesired stimulation. Similarly, exercise caution for use of this feature in patients with a history of obstructive sleep apnea, shortness of breath, coughing, swallowing difficulties, or aspiration.

6. Environmental and Medical Therapy Hazards

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a 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 manuals.

For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the generator in the chest.

Therapeutic radiation may damage the 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 generator.

Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the generator.

Magnetic resonance imaging (MRI) should not be performed using a transmit RF body coil for certain VNS therapy device configurations or under certain specific conditions. In some cases, heating of the lead caused by the transmit RF body coil during MRI may result in serious injury. Static, gradient, and radio frequency (RF) electromagnetic fields associated with MRI may change the generator settings (i.e., reset parameters) or activate the VNS device if the Magnet Mode output remains "ON". Note that certain magnetic resonance (MR) system head coils operate in receive-only mode and require use of the transmit RF body coil. Other MR systems use a transmit/receive RF head coil. Local or surface coils may also be receive-only RF coils that require the transmit RF body coil for MRI. **The use of a receive RF coil does not alter hazards of the transmit RF body coil.** Exposure of the VNS Therapy System to any transmit RF coil must be avoided. Do not perform MRI scans using any transmit RF coil in the defined exclusion zones. See *MRI with the VNS Therapy System* instructions for use for details or further instructions for special cases such as lead breaks or partially explanted VNS Therapy systems.

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

If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the generator should be set to 0 mA or function of the generator should be monitored during initial stages of treatment.

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

For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals.

7. Adverse Events — Epilepsy

Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order: ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); dyspnea (difficulty breathing, shortness of breath); hypesthesia (impaired sense of touch); increased coughing; infection; insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting.

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[1] The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician's manuals. (Copies of VNS Therapy physician's and patient's manuals are posted at www.livanova.com.) The information is not intended to serve as a substitute for a 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.