The ***nerve*** to expect more.

The ***nerve*** to give your patients a different path forward.

Enable your pediatric patients with drug-resistant epilepsy to achieve their full potential

LivaNova Epilepsy | VNS Therapy®

The ***nerve*** to move beyond medication

There's no denying the efficacy of anti-seizure medications (ASMs) for epilepsy. But when managing drug-resistant epilepsy (DRE), medications alone won't be enough to help your patients achieve seizure control or provide an improved quality of life. That's why it's critical you consider non-drug options and speak to your patients about them as soon as you suspect DRE. After all, the sooner you act, the more likely you are to mitigate the serious consequences of DRE.

Addressing the risks of uncontrolled seizures requires a proactive treatment strategy

Children with drug-resistant epilepsy who are treated with ASMs alone could suffer from developmental deterioration that **impacts motor and social function**.[1]

5.2×

Pediatric patients who do not achieve seizure freedom for 5 years were at a **5.2× greater risk of SUDEP** (95% CI 1.4-18.5)[2]

Fewer than 1 in 10 patients achieves seizure freedom with an ASM after 2 or more failures[3]

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.

Please see brief summary for the VNS Therapy System located in the back pocket.

The ***nerve*** to redefine patient expectations

VNS Therapy® is a proven treatment option for DRE, indicated for patients as young as 4 years old. With the latest SenTiva® generator and the easy-to-use programming system, you can set an automatic titration schedule, visualize patient trends, and receive feedback to help customize treatment to best fit your patient's therapeutic needs.

VNS Therapy works differently to help patients achieve seizure control

VNS Therapy stimulates the vagus nerve, sending mild electrical pulses to the brain to **help prevent seizures before they manifest**[4]

Uses an implantable generator and lead and can be programmed to **fit the needs of a patient's individualized treatment strategy**[4]

1-2 HRS

Unlike invasive brain surgeries, VNS Therapy involves a **short outpatient procedure that usually takes 1 to 2 hours**[4]

Treatment is delivered automatically, **maximizing adherence** for optimal seizure control[4]

VNS Therapy controls seizures in 3 ways

Normal Mode
Preventative

Helps prevent seizures by delivering treatment at regular intervals all day, every day[4]

AutoStim Mode
*Responsive**

Helps stop or shorten a seizure by responding to a rapid increase in heart rate, a proven seizure biomarker[4-6]

Magnet Mode
On-Demand

Helps stop or shorten a seizure once it starts by passing the included VNS Therapy Magnet over the generator[4]

See VNS Therapy in action at **HowVNSWorks.com**

*Only available in models 106 and 1000.

The ***nerve*** to enable patients to overcome seizures

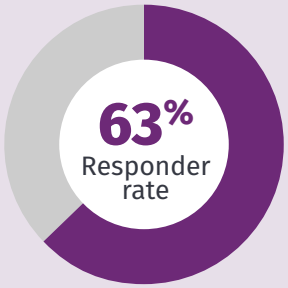
The latest generation of VNS Therapy is designed with seizure control in mind, with the ability to customize treatment to meet your patient's needs. Responsive VNS Therapy with AutoStim may also provide enhanced seizure control and earlier onset of effect.

Early use of VNS Therapy can help improve long-term outcomes at a critical time in a patient's development

Patients treated earlier in their disease were nearly **3× more likely to be seizure-free** compared to those patients who delayed VNS Therapy (N=89, follow-up at 12 months).[7]

VNS Therapy reduces the frequency, duration, and severity of seizures and improves post-ictal recovery

Patients with ≥50% reduction in seizure frequency[8]



At 24 months on stable ASM regimen
(N=83)

In a study among 347 pediatric patients followed for 24 months[8]:

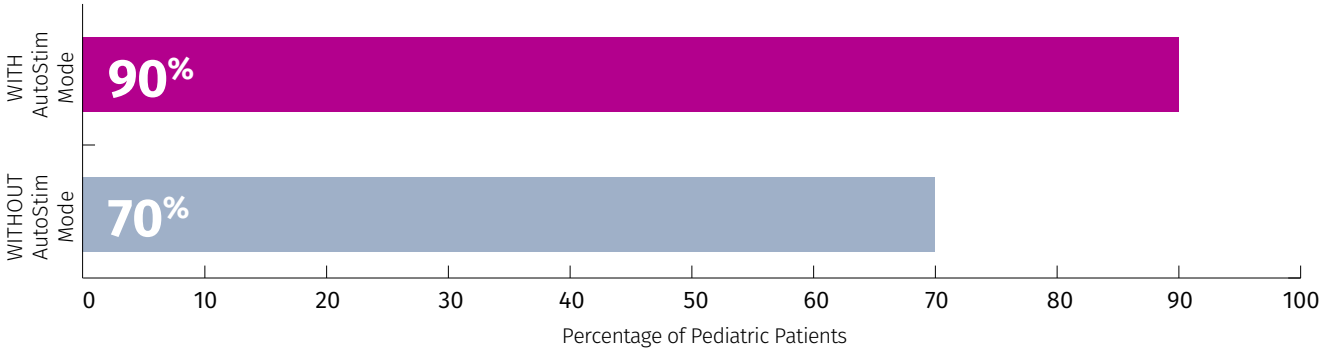
48% experienced **shorter seizures**

42% experienced a **reduction in seizure severity**

40% experienced an **improvement in post-ictal recovery**

VNS Therapy with AutoStim can provide better seizure control

Proportion of VNS Therapy patients who experienced a ≥50% reduction in seizure frequency[9]



N=10, follow-up of 12 months

The ***nerve*** to relieve the burden of adverse effects

VNS Therapy has proven to be a safe, well-tolerated adjunctive treatment option that can improve your patients' seizure control without contributing to ASM toxicity. As an adjunctive treatment with no drug interactions, it can safely be combined with any ASM regimen to maximize seizure control and minimize side effects.

VNS Therapy has proven safety and tolerability

The most common side effects occur only during stimulation and typically diminish over time[10,11]

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%

VNS Therapy has **no neurotoxic effects or drug interactions[10,12]**

"I began taking a number of medications to help with the seizures, but there were a lot of side effects. My parents noticed the medications were making me act aggressive and anxious. They also made me more forgetful, and I felt depressed since I was struggling with schoolwork.

After VNS Therapy, I was able to cut down to only two medications. My only side effect was occasional hoarseness, but that has improved over time."

– Andre, a real patient diagnosed with DRE at 11 and treated with VNS Therapy at 16*

*This is the experience of an individual who has been treated with VNS Therapy. Individual results may vary.

The ***nerve*** to enhance a patient's quality of life

Your patients with DRE deserve the opportunity to reach their developmental potential—and VNS Therapy has helped many of them do just that. VNS Therapy has shown to offer quality-of-life (QOL) benefits that can help patients overcome the obstacles they face in everyday life.

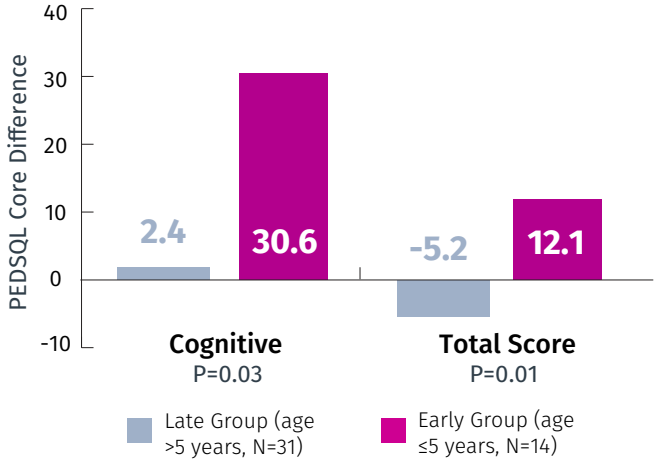
VNS Therapy empowers patients with meaningful quality-of-life benefits

1 out of 2 PATIENTS experienced an improvement in concentration and energy[8]

2 out of 3 PATIENTS experienced an improvement in alertness[8]

3 out of 4 patients experienced improvements in overall quality of life[14]

Difference between pre- and postoperative PEDSQL results in early vs. late implantation[13]



Patients on VNS Therapy experienced reductions in health-related events and medication dependence

3× reduction of status epilepticus in adolescents (12-17 years of age)[15]
(N=207, mean follow-up at 29.9 months [±9.4 months])

While on VNS Therapy, 2 out of 3 children taking benzodiazepines completely eliminated them from their regimen[16]

For patients on VNS Therapy, SUDEP rates decreased over time

32% reduction in rates of SUDEP

In a retrospective analysis, age-adjusted SUDEP rates decreased over time from years 1 to 2 (2.47/1000 person-years) to years 3 to 10 (1.68/1000 person-years).[17]

PEDSQL=pediatric quality of life; SUDEP=sudden unexpected death in epilepsy.

The ***nerve*** to trust 25 years of real-world experience

VNS Therapy is built on a legacy that spans over 2 decades. With over 1 million patient-years of treatment experience, it's easy to see why so many physicians choose to treat DRE with VNS Therapy.

#1

#1 prescribed device for treating DRE[18]

125,000+

125,000+ patients treated, including **35,000 children**[18]

4+ years

Only DRE neurostimulation therapy **indicated to treat children as young as 4 years old**[4]

75% of patients chose to replace their device at the end of service[18]

My definition of treatment success in patients with drug-resistant epilepsy is when their seizure frequency, seizure severity, their seizure duration, as well as the post-ictal period improve—but also when their quality of life starts to improve, when they are more adherent to their treatment, and when they have better overall side effects from their treatment.

– Dr. Ahmed Abdelmoity, *Pediatric Epileptologist*

The ***nerve*** to discover the benefits of VNS Therapy

Enables **better seizure control**

- Reduces frequency of seizures[8,9]
- Lessens the severity and duration of seizures[8]
- Improves post-ictal recovery[8]

Relieves the burden of adverse effects

- No neurotoxic effects or drug interactions[10,12]
- Most common adverse effects diminish over time[10,11]

Provides meaningful **quality-of-life benefits**

- Significantly improves overall QoL and cognitive outcomes[8,13]
- Lowers the risk of health-related events and medication dependence[15,16]
- SUDEP rates decreased over time[17]

Built on a legacy of **real-world experience**

- 125,000+ patients treated, including 35,000 children[18]
- 75% of patients chose to replace their device at the end of service[18]
- Only DRE neurostimulation therapy indicated to treat children as young as 4 years old[4]

Learn how VNS Therapy can help your patients at **NerveToExpectMore.com**

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IM-7600395-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.