VNS Therapy™

Clinical Paper Summary

VNS Therapy™ Parameters for Clinical Response in Epilepsy

Fahoum, F., Boffini, M., Kann, L., Faini, S., Gordon, C., Tzadok,M., & El Tahry, R. (2022).
VNS parameters for clinicalresponse in Epilepsy. Brain stimulation.

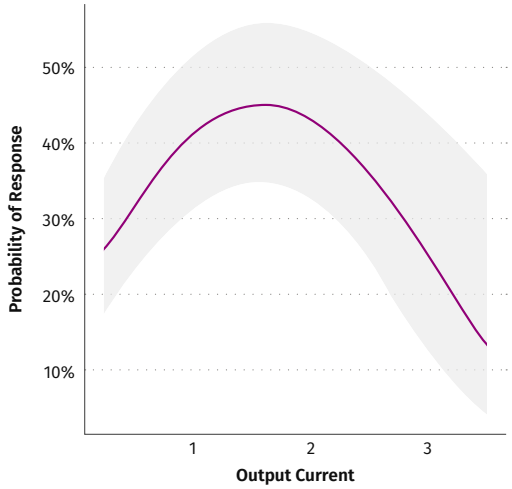
Key Take Away 1

Retrospective analysis of VNS Therapy™ parameters revealed a dose of VNS for epilepsy associated with seizure frequency reduction that lies within the target range in the product labeling. Patients titrated near this dose experienced greater seizure frequency reduction than those titrated above or below it.

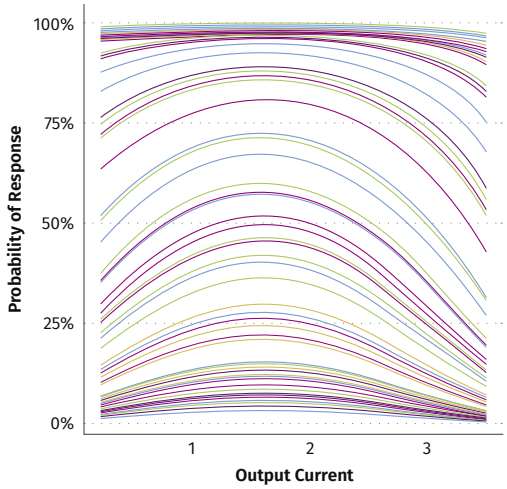
	N	12-month Responder Rate	Median Seizure Reduction
Output Current <1 mA	44	36%	34.46%
Output Current 1.5-1.75 mA	392	47%	43.27%
Output Current >= 2.5 mA	32	41%	32.76%

Clinical outcomes of people with VNS titrated to settings near the model-selected dose of 1.625mA. Patients in each group were selected to have the listed output current at any pulse width at 12-months of follow up. The response rate was calculated at 12 months after implant.

Mean Predicted Probabilities of Response



Individualized Predicted Probabilities of Response



A Generalized Linear Mixed Model (GLMM) was used to identify relationships between both VNS parameters and demographic features to clinical response (≥50% reduction in seizures). This is a population-level outcome, indicating that some patients will require VNS intensities above or below this value. The left figure demonstrates the population level mean and standard deviation of outcomes predicted by the GLMM. The right figure displays the model's predicted outcome for several hypothetical patients with specific demographic parameters.

Key Take Away 2

VNS responders titrated to the appropriate VNS parameters at or before 12 months after implant had a durable response to the therapy at future follow-up. Those who stayed at settings within the 1.5mA-1.75mA range had the highest likelihood of prolonged response to VNS.

	N (Unique Visits After 12 Months)	Responder Rate	Median Seizure Frequency Reduction
Output Current <1.5 mA	7	71%	100%
Output Current 1.5-1.75 mA	209	87%	86.13%
Output Current > 1.75 mA	98	80%	75.72%

Long-term clinical outcomes of VNS responders titrated to the target intensity of VNS (1.5mA – 1.75mA) by 12 months after implant (n = 184 subjects). Patients initially titrated to this dose may have increased or decreased their VNS dose at follow up visits after 12 months.

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Study Summary

Objective

Significant variance in VNS Therapy™ parameter settings was detected in post-market surveillance of VNS Therapy management. The most recent VNS guidelines from the American Academy of Neurology recommended further investigation of VNS parameters could improve the quality of VNS management and patient outcomes[1]. This analysis was undertaken with the purpose to provide an evidence -based justification of a target dose of VNS Therapy to improve epilepsy outcomes.

Method

A total of 1178 subjects from LivaNova-sponsored clinical studies were assessed for this work. A generalized linear mixed model was employed to assess the correlation between programming settings and demographic features and clinical response (defined as a 50% reduction in seizure frequency). This regression model was selected because it is known to be suitable when there is non-independence between observed values, such as when a single patient contributes multiple data points toward an outcome. The model included quadratic factors for output current and duty cycle, which were modeled as continuous variables, while pulse width and signal frequency were modeled as categorical variables due to a limited number of available settings.

Results

The mixed model successfully accounted for 86% of the variance in the database population, indicating a robust model fit with appropriate variable selection. A population level output current and duty cycle were identified as correlating with a peak level of response to VNS Therapy. The model did not find that any of the pulse widths or signal frequencies assessed had a significant impact on response.

While the outcome of this analysis differs slightly from the manufacturer's labeling, it can be said to generally confirm the target dose range recommended in the VNS Therapy System Epilepsy Physician's Manual, and patients who do not respond at the introductory duty cycle of 10% should have their duty cycle increased. This outcome was independent of a time effect, indicating that even patients who have been under-dosed for some time could still benefit from achieving the target dose. Post-hoc analysis further indicated that patients who were programmed to the target dose and kept there tended to stay in response (>85% likelihood).

Conclusion

This analysis supports wider adoption of current dosing recommendations, and specifically the use of target output currents within the range defined in the VNS Therapy System Epilepsy Physician's Manual. There are no robust data available at present to advocate for the use of frequencies other than 20, 25, or 30 Hz in epilepsy for the purpose of maximizing clinical response. While there appears to be a positive e ect of duty cycle on seizure reduction, duty cycle should be increased only if patients do not respond at 10% duty in favor of battery savings.

Limitations

The principal limitation of this retrospective analysis is that it utilized data collected from a variety of clinical studies of VNS Therapy. The studies included interventional and observational designs, different follow-up durations, targeted patients of slightly different demographic profiles, and the methods for data collection were not uniform across all studies. None of these studies were prospectively designed for the purpose of assessing the relationship between VNS Therapy parameters and clinical response.

Click here or scan the QR code to read the full paper

[1]Morris, G. L., Gloss, D., Buchhalter, J., Mack, K. J., Nickels, K., & Harden, C. (2013). Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology, 81(16), 1453-1459.

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VNS Therapy™

Brief Summary[1] of Safety Information for the VNS Therapy™ System

[Epilepsy Indication] (December 2022)

1. INTENDED USE / INDICATIONS

Epilepsy (ANZ)—The VNS Therapy System (exclusive of SenTiva™) is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to seizure medications. AspireSR™ features an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.
The SenTiva™ pulse generator 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 (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications. SenTiva features an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

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" chapter 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 manual. 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 encounteredduring a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared tofollow 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 are at greater risk for 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 nervestimulation may also cause new onset sleep apnea in patients who have not previously been diagnosedwith 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 (i.e., one that occurs when "ON" time is greater than "OFF" time) and high frequency stimulation (i.e., stimulation at ≥50Hz) 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.
The Wand, Programmer, and patient magnet are MR unsafe devices. These devices are projectile hazards and must not be brought into the MR scanner room.
Generators with AutoStim only — The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias or who are using 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)].

4. WARNINGS — EPILEPSY

The VNS Therapy System should only be prescribed and monitored by physicians who have specifictraining 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 depression or epilepsy and should be familiar with the programming and use of the VNS Therapy System.
Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System.
The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS 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(<12 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 pulse generator turns the device OFF (output current = 0 mA). For Model 100, 101, 102 and 102R resetting the pulse generator will result in device history loss.
Patients who smoke may have an increased risk of laryngeal irritation.
Generators with AutoStim only — For devices that sense changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc.
Generators with AutoStim only — For the AutoStim feature, the physical location of the device critically affects this its ability to properly sense heart beats. Therefore, care must be taken to follow the implant location selection process outlined in the Implantation Procedure. Note that this implant location selection procedure may be performed preoperatively as part of the patient's surgical work-up.
SenTiva 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. 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 the 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); hypoesthesia (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. Adverse events reported in clinical investigation of the AutoStim feature were comparable.

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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.

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