

Vagal Nerve Stimulator (VNS)

Last updated: February 8, 2023

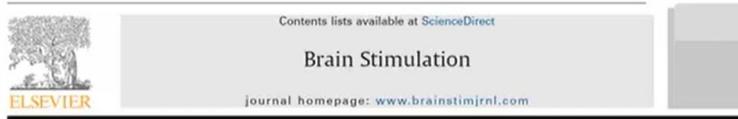
COMPARISON OF NEUROMODULATIONS (RNS, DBS, VNS) – see p. E11 >>

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Transcutaneous VNS

Transcutaneous vagus nerve stimulation

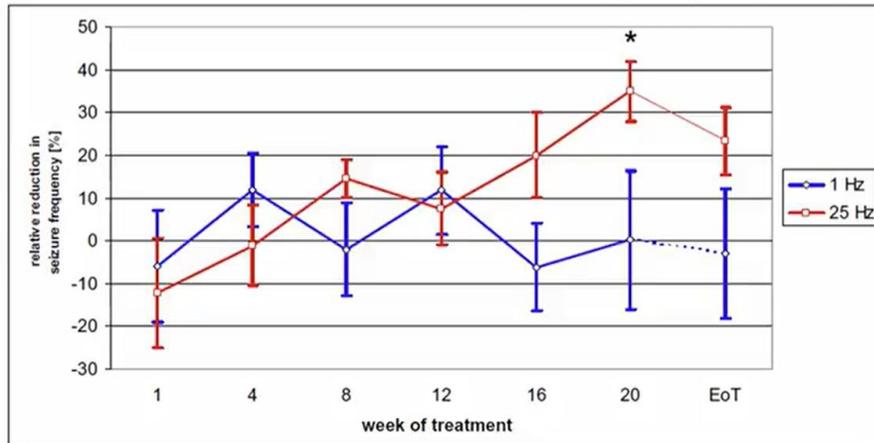


Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02)

S. Bauer^{a,b,*}, H. Baier^c, C. Baumgartner^d, K. Bohlmann^e, S. Fauser^f, W. Graf^g, B. Hillenbrand^h, M. Hirschⁱ, C. Last^j, H. Lerche^k, T. Mayer^l, A. Schulze-Bonhage^l, B.J. Steinhoff^h, Y. Weber^k, A. Hartlep^m, F. Rosenow^{a,b,l}, H.M. Hamer^{z,1}



Figure 1 Left side: programmable stimulation device and ear electrode. Right side: placement of ear electrode in the ear conch.



Surgical VNS

VNS - palliative continuously intermittent electrical stimulation with chest-implanted pacemaker-like device.

- FDA approved in 1997.

MANUFACTURER

- first models were made by **Cyberonics company** >>



- now made by **LivaNova company** >>



BROCHURES

Cyberonics >> → LivaNova >> also >>
Full Manual >>

Read!!!! >>

Reading

J. Wheless, A. Gienapp, P. Ryvlin. Vagus nerve stimulation (VNS) update. *Epilepsy Behav*, 88 (2018), pp. 2-10

P. Ryvlin, E.L. So, C.M. Gordon, D.C. Hesdorffer, M.R. Sperling, O Devinsky, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia*, 59 (2018), pp. 562-572

Brodie MJ. *Curr Neurol Neurosci* 2016

INDICATIONS

- 1) **focal-onset** epilepsy (even with anatomically defined single foci); **FDA approval (1997)**: “*adjunctive therapy for reducing the frequency of seizures in patients > 4 years with partial-onset seizures refractory to antiepileptic medications*”
 - some insurances may deny if not for "partial epilepsy" (ICD-10 codes: G40.211 / G40.219 / G40.011 / G40.019 / G40.111 / G40.119)
 - Medicare / CMS National Coverage Determination (NCD) 160.18 for VNS states: "Effective for services performed on or after July 1, 1999, VNS is reasonable and necessary for patients with *medically refractory partial onset* seizures for whom *surgery is not recommended or for whom surgery has failed.*"
 - reports of implantation in 1 year-old patient (word of caution – as child grows, the lead may start pulling on vagus nerve – cases of bradycardia that resolved after lead replacement)
 - 2) mounting evidence suggests effectiveness in **generalized** epilepsy (VNS is treatment of choice for **Lennox-Gastaut syndrome**)
 - N.B. *on label* is only for **partial** epilepsy! (*off label* can use for **generalized** epilepsy – VNS works very well!!!)
 - VNS has been claimed to effectively control **atonic seizures** as an alternative to corpus callosotomy (meta-analysis of 31 studies involving 533 children showed that **callosotomy** was more effective than VNS at a cost of greater adverse events, including twice as many reoperations and a 14% rate of symptomatic disconnection syndrome).
 - 3) **FDA approved (2007)** as adjunctive long-term treatment of chronic / recurrent depression in patients > 18 years with a **major depressive episode** not adequately relieved by ≥ 4 antidepressant treatments
 - N.B. improvement in mood may be a huge additional benefit for epilepsy patients!
 - depression prevalence is 13–37% of patients with epilepsy (number is higher in uncontrolled epilepsy).
 - antidepressive effect is independent of seizure benefit.
- stimulation of either vagus nerve is effective, but **left nerve is always chosen** (less likely to cause cardiac effects), usually **left cervical vagus nerve**.
 - if left nerve unavailable, there are case reports of implantation on the **right** side without side effects.

N.B. VNS can be combined with RNS, DBS.

VNS, RNS, and DBS are all palliative and comparable in efficacy, both in pivotal trials and over longer-term trials. VNS is often a first choice as it is extracranial.

INVESTIGATIONAL

Heart failure - Autonomic Regulation Therapy (ART) delivered through VNS. ART is being studied in a clinical trial called **ANTHEM-HFrEF**.



CONTRAINDICATIONS

1. Absence of vagus nerve
2. Absence of epilepsy
3. Not surgical candidate

MECHANISM OF ACTION

- 20-40% of vagus fibers are **efferent** – cause **side effects**;
 nucleus ambiguus → skeletal laryngeal musculature, bradycardia or heart block.
 dorsal nucleus of the vagus → GI side effects and anorexia.

CARDIOPROTECTION

- VNS stimulation reduces T-wave alternans via anti-adrenergic effects, improved baroreflex sensitivity, anti-inflammatory / anti-apoptosis effects.

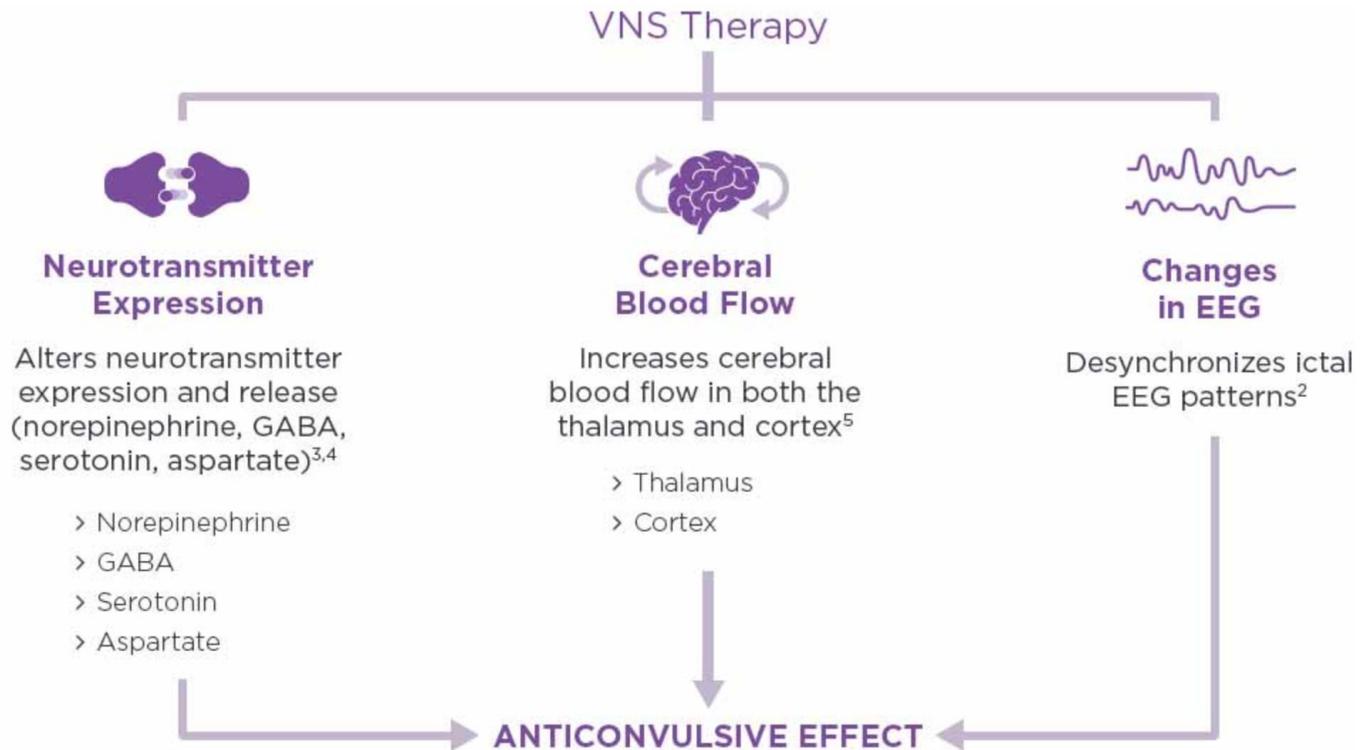
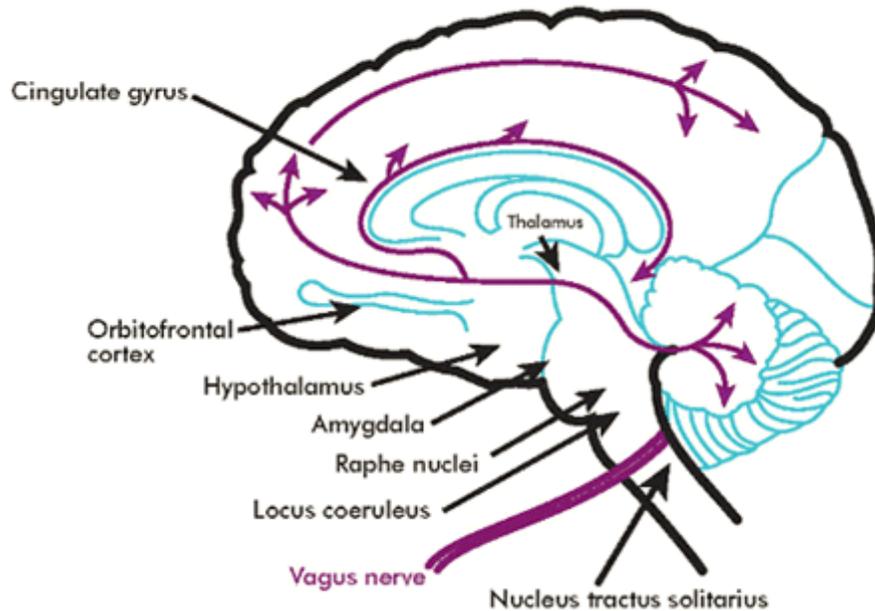
Epilepsy ≈ 3-fold increased risk of lethal cardiac arrhythmias!

SEIZURES

- 80% of vagal fibers are afferent → synapse mainly onto the **nucleus of the solitary tract** → **locus coeruleus** and **dorsal raphe** → ↑CNS noradrenergic tone (NE is anti-epileptic)
- project to many structures in brain (incl. hippocampus, amygdala, thalamus).
 - changes are seen in thalamic blood flow that correlate with efficacy.
 - decline in interictal spikes can be seen on serial EEGs with chronic VNS.

- SPECT shows normalization of GABA_A receptor density in patients with good response to 1 year of VNS stimulation.

Pathways affected by VNS:



2. Koo B. J Clin Neurophysiol. 2001; 434-441. 3. Roosevelt et al. Brain Res. 2006; 124-132. 4. Ben-Menachem et al. Epilepsy Res. 1995;221-227. 5. Vonck et al. Seizure. 2008.05.001.

VNS efficacy**E03 trial (multinational)****E05 trial (US only)****Microburst VNS therapy**

- high frequency bursts of electrical stimulation, called microbursts.

Animal study - rCBF

Martlé V et al. Regional brain perfusion changes during standard and microburst vagus nerve stimulation in dogs. Epilepsy Res. 2014 May;108(4):616-22.

VNS Therapy System was implanted in ten Beagle dogs. μ -SPECT was performed after sham, standard and microburst VNS in a randomized, cross-over study. Nineteen volumes of interest (VOIs) were semi-quantitatively analysed and perfusion indices (PIs) were calculated. Furthermore, a rostro-caudal gradient (R-C), an asymmetry index (AI) and a cortical-subcortical index (Co-SCo) were determined. The SPECT results after standard and microburst VNS were compared pairwise with sham stimulation.

RESULTS:

Acute standard VNS did not cause significant rCBF alterations. Acute microburst VNS caused a significant hypoperfusion in the left frontal lobe ($P=0.023$) and in the right parietal lobe ($P=0.035$). Both stimulation paradigms did not cause changes in R-C, AI nor Co-SCo.

CONCLUSIONS:

Microburst VNS is more potent than standard VNS to modulate the rCBF in the dog. Our results promote further research towards the antiepileptic effect of microburst VNS in dogs and humans.

Animal study - transmitter

Martlé V et al. The effect of vagus nerve stimulation on CSF monoamines and the PTZ seizure threshold in dogs. Brain Stimul. 2015 Jan-Feb;8(1):1-6.

OBJECTIVE:

We aimed to investigate the effect of two rapid cycling VNS paradigms on CSF monoamine levels and the seizure threshold in the canine pentylenetetrazole (PTZ) model.

METHODS:

Eight Beagle dogs, implanted with a VNS Therapy(®) System, participated in a cross-over study. Levels of serotonin (5HT), norepinephrine (NE) and dopamine (DA) were quantified in the CSF after 1 h of sham, standard and microburst VNS with a wash-out period of 1 month. One week after the CSF experiment, the PTZ seizure threshold was determined after the same stimulation paradigm. As a positive control, the PTZ seizure threshold was determined after a single oral dose of phenobarbital.

RESULTS:

Rapid cycling standard and microburst VNS caused a significant increase of NE levels in the CSF ($P = 0.03$ and $P = 0.02$ respectively). No significant changes in 5HT or DA levels were detected. Rapid cycling standard and microburst VNS did not cause significant changes in the PTZ seizure threshold compared to sham.

CONCLUSIONS:

VNS induces an increase of NE in the canine brain, which supports previous findings indicating that VNS influences the locus coeruleus-NE (LC/NE) system. Importantly, this study demonstrates that this increase in NE is measurable in the CSF. One hour of VNS did not affect seizure threshold in the canine PTZ model. Therefore, the role of NE in the antiepileptic effect of VNS in dogs remains to be elucidated.

Animal study – heart rate

Martlé V et al. Evaluation of heart rate variability in dogs during standard and microburst vagus nerve stimulation: a pilot study. Vet J. 2014 Dec;202(3):651-3.

The present study investigated heart rate variability (HRV) in healthy Beagle dogs treated with 1 h of sham, standard or microburst left-sided VNS in a crossover design. No significant differences were found between the stimulation paradigms for any of the cardiac parameters. Short-term left-sided VNS, including a novel bursting pattern (microburst VNS), had no statistically significant effect on HRV in ambulatory healthy dogs.

Humans - Feasibility Study

ClinicalTrials.gov Identifier: NCT03446664

Principal Investigator: Selim Benbadis, MD University of South Florida Health

Contact: Amy Keith 281-228-7495 Amy.keith@livanova.com

Contact: Jeffrey Way 281-228-7394 Jeffrey.way@livanova.com

Estimated Enrollment : 40 participants
Intervention Model: Single Group Assignment
Intervention Model Description: Two cohorts of subjects with refractory epilepsy; (1) subjects with **primary generalized** tonic-clonic seizures and (2) subjects with **partial onset** seizures including complex partial seizures with or without secondary generalization.
Masking: None (Open Label)
Primary Purpose: Treatment
Actual Study Start Date : February 27, 2018
Estimated Primary Completion Date : April 2021
Estimated Study Completion Date : June 2021

Primary Outcome Measures

Efficacy Primary Endpoint: Percent change from baseline in seizure frequency [Time Frame: Up to 12 months study visit]

the change in the seizure frequency per month compared to baseline will be evaluated for each subject at follow-up visits month 6 and 12.

Safety Primary Endpoint: Occurrence of stimulation related Adverse Events [Time Frame: Up to 12 months study visit]

Assess stimulation/device related adverse events at follow-up visits month 6 and 12.

Secondary Outcome Measures

Change from baseline in **seizure frequency** per month based on seizure diary provided by the sponsor [Time Frame: Up to 12 months study visit]

Change from baseline in **seizure severity** [Time Frame: Up to 12 months study visit] - as measured by the Seizure Severity Questionnaire (SSQ) scale (Cramer, 2002).

Change from baseline in **quality of life** [Time Frame: Up to 12 months study visit] - as measured by the QOLIE-31-P for adults 18 years and older (Cramer et al.; 1998) and QOLIE-AD-48 for adolescents 12 to 17 years (Cramer et al.; 1999).

Change from baseline in **antiepileptic drug (AED) load** [Time Frame: Up to 12 months study visit]

Estimated as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD) ratios for each AED included in the treatment regimen (Deckers et al., 1997), where DDD (WHO ATC/DDD index) corresponds to the assumed average therapeutic daily dose of a drug used for its main indication.

Suicidality as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) [Time Frame: Up to 12 months study visit]

All adverse events [Time Frame: Up to 12 months visit]

Eligibility Criteria

Ages Eligible for Study: 12 Years and older (Child, Adult, Older Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Inclusion Criteria:

1. Clinical diagnosis of medically refractory epilepsy with primary generalized tonic-clonic seizures (limited to 20 subjects) or partial onset seizures including complex partial seizures with or without secondary generalization (limited to 20 subjects).
2. Must be on adjunctive antiepileptic medications.
3. Willing and capable to undergo multiple evaluations with functional magnetic resonance imaging (fMRI), electroencephalogram (EEG) and electrocardiogram (ECG).
4. 4(A) For subjects with partial onset seizures: An average of ≥ 3 countable seizures per month based on seizure diary during the 3 month baseline period and no seizure-free interval greater than 30 days during those 3 months.
4(B) For subjects with PGTCs: Have at least ≥ 3 countable seizures during the 3 month baseline period. Note: Each seizure within a cluster may be counted as separate seizures.
5. 12 years of age or older.
6. Subject is a male or non-pregnant female adequately protected from conception. Females of childbearing potential must use an acceptable method of birth control.
7. Provide written informed consent-assent/Health Insurance Portability and Accountability Act (HIPAA) authorization and self-reported measures with minimal assistance as determined by the investigator.

Exclusion Criteria:

1. Currently using, or are expected to use, short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy.
2. A VNS Therapy System implant would (in the investigator's judgment) pose an unacceptable surgical or medical risk for the subject.
3. A planned procedure that is contraindicated for VNS therapy.
4. **History of implantation of the VNS Therapy System.**
5. Currently receiving treatment from an **active implantable medical device.**
6. Presence of **contraindications to MRI** per the MRI subject screening record.
7. Known clinically meaningful **cardiovascular 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).
8. History of **chronotropic incompetence** (commonly seen in subjects with sustained bradycardia [heart rate < 50 bpm]).
9. **Cognitive or psychiatric deficit** that in the investigator's judgment would interfere with the subject's ability to accurately complete study assessments.
10. History of **status epilepticus within 1 year** of study enrollment.

11. **Dependent on alcohol or narcotic drugs** as defined by DSM IV-TR within the past 2 years, based on history. Tests for drug or alcohol use will not be administered.
12. Currently being treated with prescribed medication that contains **cannabis or cannabis related** substance.
13. Any history of **psychogenic non-epileptic seizures**.
14. Currently participating in another clinical study without LivaNova written approval.

DEPRESSION

Scott T. Aaronson et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psych. Published Online:31 Mar 2017 >>

- 5-year, prospective, open-label, nonrandomized, observational registry study
- 61 U.S. sites, 795 patients.
- inclusion - treatment-resistant depression:
 - a) major depressive episode (unipolar or bipolar depression) of at least 2 years' duration
 - b) ≥ 3 depressive episodes (including the current episode)
 + failed ≥ 4 depression treatments (including ECT).
- exclusion - history of psychosis or rapid-cycling bipolar disorder.
- primary efficacy measure - response rate = decrease of $\geq 50\%$ in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score at any postbaseline visit during the 5-year study.
- secondary efficacy measure - remission.
- results - VNS group had better clinical outcomes:
 - **5-year cumulative response rate** 67.6% (vs. 40.9%).
 - **cumulative first-time remitters** 43.3% (vs. 25.7%).
 - subanalysis of **history of response to ECT**:
 - positive response to ECT- 5-year cumulative response rate 71.3% (vs. 56.9%).
 - no response to ECT - 59.6% (vs. 34.1%).
- conclusions - adjunctive VNS has enhanced antidepressant effects compared with treatment as usual.

Pending read

¹George MS, Rush AJ, et al. A One-Year Comparison of Vagus Nerve Stimulation with Treatment as Usual for Treatment-Resistant Depression. *Biol Psychiatry* 2005;58:364-373

²Sackeim HA, Brannan SK, et al. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol.* 2007;Feb 9:1-10

HARDWARE (LEADS)

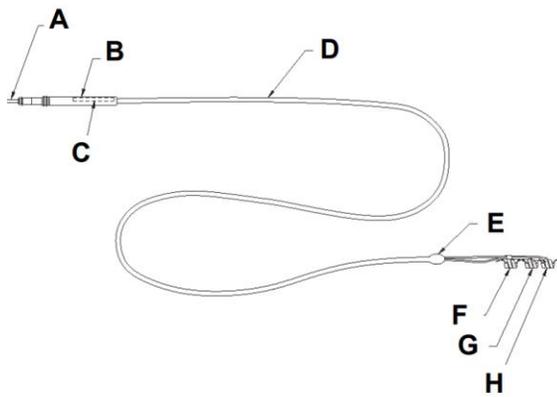
Only **dual-pin** lead is **model 300** – no longer manufactured

Lead characteristics:

Lead Model	302	303	304
Insulation	Silicone	Silicone	Silicone
Length*	43 cm	43 cm	43 cm
Resistance	180 to 250 ohms, pin to electrode	180 to 250 ohms, pin to electrode	120 to 180 ohms, pin to electrode
Conductor Material	Platinum Iridium	Platinum Iridium	Platinum Iridium

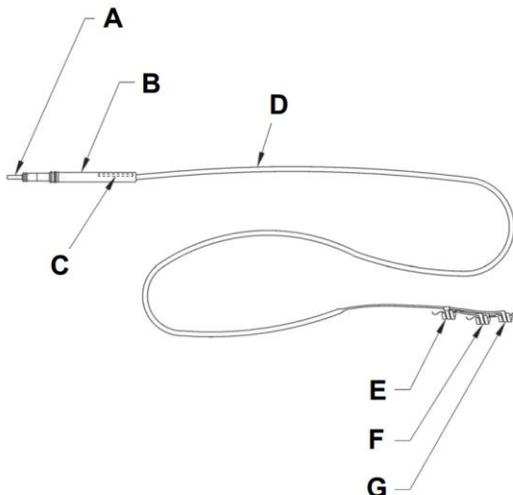
List price for 304 – 8,068 USD (2020 March)

Model 302 and 304 Lead



- A** Connector Pin
- B** Lead Connector
- C** Model/Serial Number Tag
- D** Lead Body
- E** Electrode Bifurcation
- F** Anchor Tether
- G** Electrode (+) (White Suture)
- H** Electrode (-) (Green Suture)

Model 303 Lead



- A** Connector Pin
- B** Lead Connector
- C** Model/Serial Number Tag
- D** Lead Body
- E** Anchor Tether
- F** Electrode (+) (White Suture)
- G** Electrode (-) (Green Suture)

VNS THERAPY (MODEL 302)

PERENNIADURA (MODEL 303)

PERENNIAFLEX (MODEL 304)

<p>Conformance to Standards American National Standards Institutes (ANSI) & Association for the Advancement of Medical Instrumentation (AAMI) NS15: Implantable peripheral nerve stimulators EN 45502-1, Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer</p>		<p>Electrodes and Anchor Tether Helical material: Silicone elastomer* Conductor material: Platinum/Iridium Alloy Separation: 8 mm (.31 in) center to center Suture material: Polyester</p>	
<p>Lead Connector Diameter: 3.2 mm (.127 in) Material: Silicone*</p>		<p>Inner Diameter of Helix Model 304-20: 2 mm (.08 in) inner diameter Model 304-30: 3 mm (.12 in) inner diameter</p>	
<p>Connector Pin Diameter: 1.27 mm (.05in) Material: 300 series stainless steel</p>		<p>Tie-Downs Dimensions: 5.7 mm x 7.7 mm (.22 in x .30 in) Material: Radiopaque silicone*</p>	
<p>Connector Ring Diameter: 2.67 mm (.105 in) Material: 300 series stainless steel</p>		<p>Connector Assembly One (1) lead connector</p>	
<p>Lead Body Diameter: 2 mm (.08 in) Insulation: Silicone* Conductor coil construction: Helical, quadfilar Conductor material: MP-35N alloy Overall length: 43 cm (17 in) Lead resistance: 120 to 180 Ohms (connector pin/ring to electrode)</p>		<p>Connector Retention Strength With VNS Therapy Pulse Generator: > 10 N</p>	
		<p>Generator Compatibility Model 102 Pulse Generator Model 103 DemiPulse Generator</p>	
<p>*Latex is not included in any component of the VNS Therapy System.</p>			

HARDWARE (COMPONENT COMPATIBILITY)

		102' Pulse™	102R' Pulse Duo™	103' Demipulse®	104' Demipulse Duo®	105' AspireHC®
Lead	300*		•		•	
	302†	•		•		•
	303†	•		•		•
	304†	•		•		•

* No longer distributed
 † Not for sale in all markets

HARDWARE (ACCESSORIES)

List price for tunneler – 506 USD (2020 March)

List price for accessory pack – 721 USD (2020 March)

HARDWARE (GENERATORS)

Currently available models are in two footprint sizes:

smaller – 103, 1000

larger – 105, 106





Generator Model	102	102R	103	104	105
Lead Compatibility	Single Pin	Dual Pin	Single Pin	Dual Pin	Single Pin
Available Since	2002	2003	2007	2007	2011
Thickness*	7 mm	7 mm	7 mm	7 mm	7 mm
Volume*	14 cc	16 cc	8 cc	10 cc	14 cc
Weight*	25 g	27 g	16 g	18 g	25 g

BATTERY CAPACITY

103, 104, 1000 - 1 Ah

102, 105, 106 - 1.7 Ah

- **self-discharge** reduces the capacity by < 1% per year.
- **battery** lasts for 10,000 hours of stimulation.
- battery performs equally at 100% and at 1% (but it is not always true clinically – sometimes when battery is < 10% patients start having worsening seizures – unexplained phenomenon that has no basis) further see >>
- **no harm leaving dead battery in** - will not leak.

LEGACY (NON-AVAILABLE)

NCP (MODELS 101, 101)

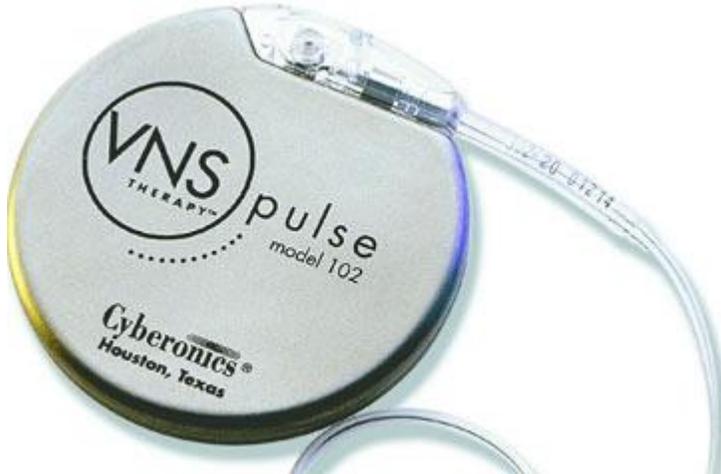


Model 100
July 1997



Model 101
January 2000

PULSE (MODEL 102)



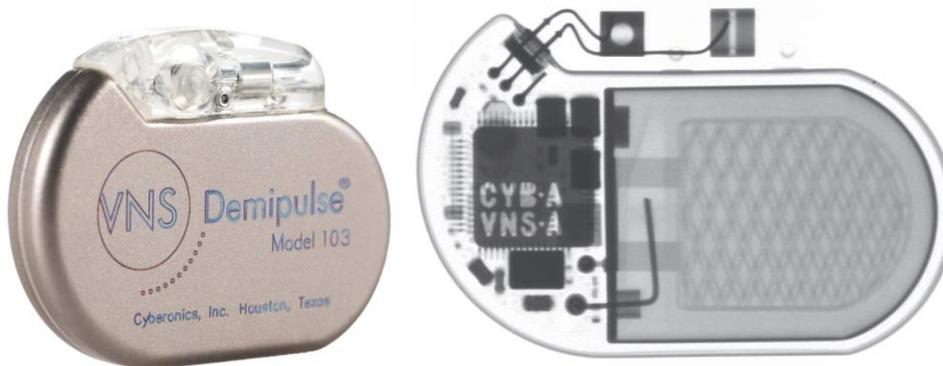
PULSE DUO (MODEL 102R DUAL PIN)



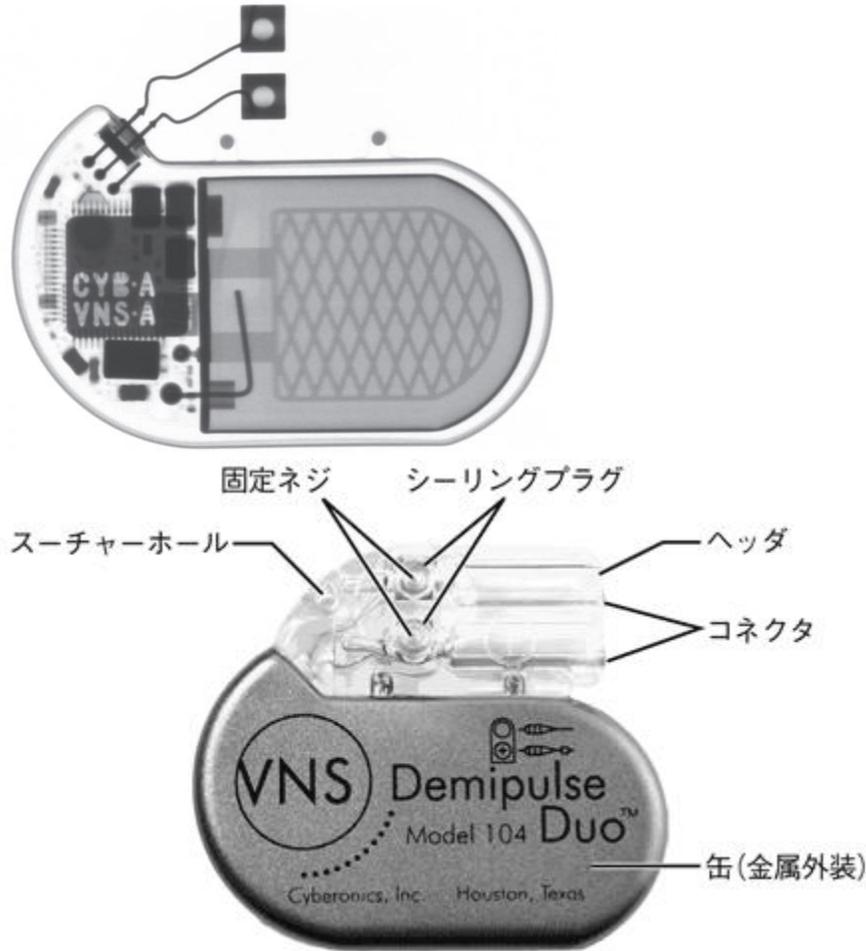
ASPIRE HC (MODEL 105)**LEGACY (STILL AVAILABLE)**

(limited for existing VNS battery replacements)

List price – 27,090 USD (2020 March)

DEMIPULSE (MODEL 103)**DEMIPULSE DUO (MODEL 104) - DUAL PIN**

List price – 27,090 USD (2020 March)

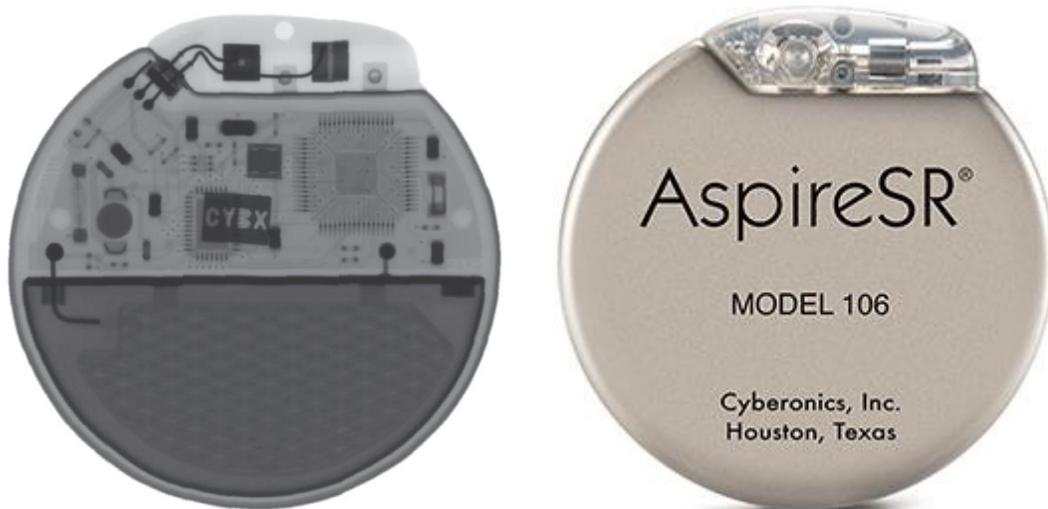


HEART RATE SENSING (AutoStim)

about AutoStim – see below >>

ASPIRE SR (MODEL 106)

List price – 31,557 USD (2020 March)



SENTIVA (MODEL 1000)

List price – 35,271 USD (2020 March)

Read 3rd page of brochure!!!! >>

December 20, 2019 | The FDA announced a recall of the LivaNova VNS Therapy SenTiva Generator due to an unintended reset error that causes the system to stop delivering VNS therapy.

<https://www.fda.gov/medical-devices/medical-device-recalls/livanova-recalls-vns-therapy-sentiva-generator-due-reset-error>

2020/03/03 LivaNova update:

- reset occurred in 0.5% of devices and only within first 60 days of enabling therapy – all outputs spontaneously reset to 0 mA.
- currently, all new devices are screened and no longer have this problem after firmware update (“LivaNova is currently distributing Model 1000 devices that have passed a LivaNova internal error screen. The error screen is intended to detect devices susceptible to unintended device disablement”).

Patients can check their Sentiva device status by entering SN (serial number):

<https://www.vnssentivareset.com>

- concerned patients also can use magnet regularly to see if device is working.



- **new features:**

1. **Low Heart Rate** detection*
2. **Prone Position** detection*
3. **Guided Programming + Scheduled Programming Titration schedule** - can be programmed during one office visit and delivered while the patient lives their life (e.g. increase stim current every 2 weeks at the specific time of the day until therapeutic target is reached).
4. **Day & Night Programming** - two independent sets of parameters can be customized and delivered based on each patient's needs.

5. **Events & Trends** - quickly view data at follow-up visits on events that may be associated with seizures.

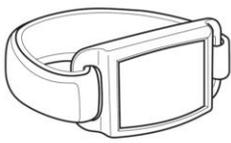
*does nothing therapeutically (does not trigger stim); activated only if device “thinks” it was a seizure (patient swiped a magnet or AutoStim went off) – bradycardia or prone position may be risk factors for SUDEP – Sentiva VNS acts as “**SUDEP monitor**”

HARDWARE – ACCESSORY KIT (#502)

- has a **screwdriver** and 4000 Ohms **test resistor**.

HARDWARE – MAGNET

The patient gets two identical VNS Therapy magnets, each providing a minimum of 50 gauss at 1 inch:



**Watch-Style
(wristband)**



**Pager-Style
(belt clip)**

HARDWARE – PROGRAMMER

- wireless wand.



- future models should have **Bluetooth technology** - device access to the patient on the personal cell phone and remote data access to the health provider.

PREOPERATIVE WORK-UP

NEW IMPLANTATION

- **ECG** – look for AV node or bundle branch blocks – high risk of cardiac side effects during VNS stimulation.

BATTERY REPLACEMENTS

- if not sure if VNS has efficacy, turn down output to 1.0 mA and watch seizure response (better strategy than letting VNS to expire and then watch – liability issue if patient goes into status).

BATTERY INDICATORS

1. **OK** - normal operating range and no special attention is required
 - 75-100%
 - 50-75%
 - 25-50%
 - 11-25%
2. **Intensified Follow-up Indicator (IFI)** - battery has depleted to a level where more frequent clinical monitoring is recommended:
 - 5-11% (model 105, 106) or 8-18% (model 103, 104)
3. **Near End of Service (NEOS)** - generator should be replaced as soon as possible.
4. **End of Service (EOS)** - generator is no longer supplying stimulation and immediate replacement is recommended. If the generator is not replaced, it will eventually lose the ability to communicate with the software

HOW TO HANDLE DEPLETING BATTERY - RECOMMENDATIONS FOR NEUROSURGEON

- see patient in clinic when battery is IFI.
- educate patient:
 - ideally, battery replacement should occur at NEOS stage.
 - every surgery has risks (incl. the risk of infection and explantation of VNS).
 - too early battery replacement:
 - 1) unnecessarily **exposes to surgical risks**
 - 2) **increases number of surgeries** in patient's lifetime
 - battery depletion can occur between office visits - recommend patients to perform a **daily magnet activation to check stimulation** (if stimulation is not felt, instruct the patient to consult with the physician to perform diagnostics testing).
- calculate time to NEOS:
 - A. **LivaNova** engineers can calculate **BLC (battery life calculated)** – you need to provide current interrogation data:

- a) call 866-882-8804
- b) email clinicaltechnicalservices@livanova.com

B. Surgeon can use **table to calculate intervals from IFI to NEOS**; e.g. for model 106 >>

- schedule battery replacement surgery near predicted NEOS time (any troubles of calculated time to NEOS – schedule frequent visits with either you or referring neurologist).
- use this waiting time to review MRIs and EEGs – it is not uncommon to encounter patients with VNS and lesional MRI:
 - a) VNS was placed inappropriately [previous provider did not recognize curable etiology of epilepsy or modern surgery was not available].
 - b) patient refused resective surgery in the past whereas modern approaches [LITT, RNS, DBS] can be more appealing to the patient today due to minimally invasive approach.
- avoid inertia when the original VNS was implanted but no efficacy was ever observed / documented; however, subsequent replacements are done “because patient has VNS and battery is low”

LEAD REVISION / BROKEN LEAD

Impedances

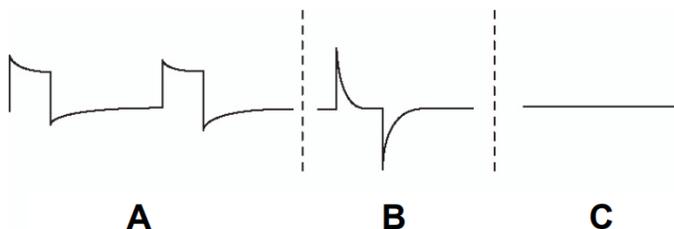
- either **too high** or **too low** (esp. < 600 Ohm).
- look for **historic impedances** – sudden changes (esp. significant decrease in impedance) are strongly suggestive.

Clinical features

- increase in seizures.
- patient perception of feeling erratic, limited, no stimulation.
- short-circuit condition - painful feeling in the neck (that stops after turning VNS off).

Diagnosis

- **X-ray**: lead discontinuities can sometimes be identified on x-ray of the VNS system.
- **ECG** – if patient is not receiving therapy (e.g. due to high impedances), it needs to be treated as new system implantation: look for AV node or bundle branch blocks preop.
- experimental - **skin electrodes** on the neck + either evoked potential monitoring equipment or an oscilloscope can be used to analyze the stimulus waveform for verification of an electrical discontinuity; differentiated waveform with narrowed pulses or no waveform at all can confirm a discontinuity:



A Intact Lead

B One Broken Lead Wire

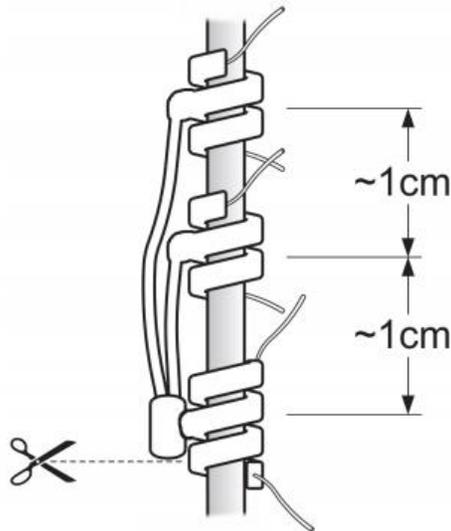
C Two Broken Lead Wires or No Output

Surgery

- no need to explant entire old lead (to jeopardize nerve) as patient's MRI conditionality will not change due to the presence of VNS system (i.e. still no MRI in exclusion zone – see below >>).
- start with low output stimulation postop (as with new system).

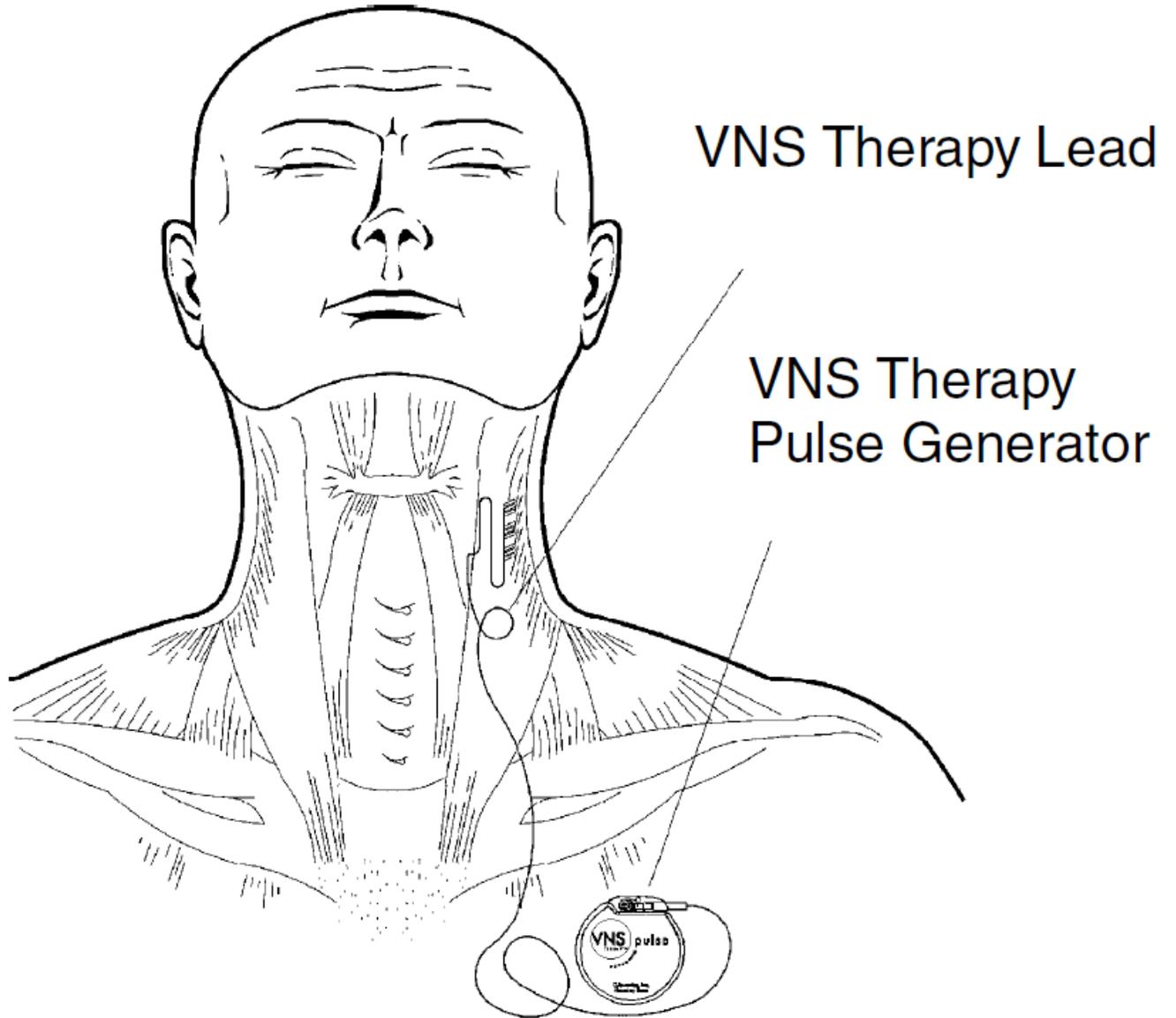
EXPLANATION OF ENTIRE SYSTEM

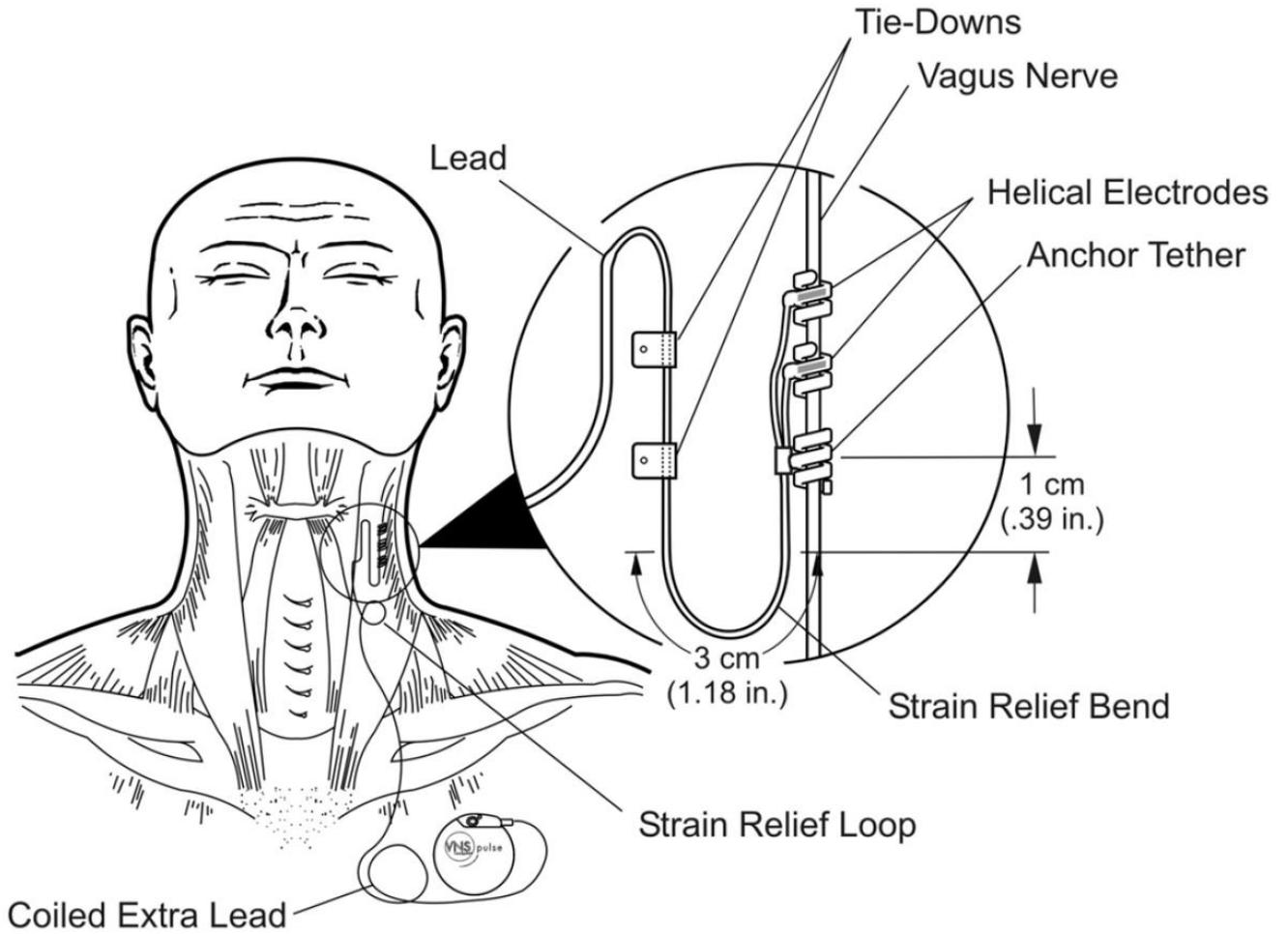
- if VNS has no efficacy, VNS is still left in situ – new IPGs in the future may offer new stimulation protocols.
- if patient insists on explantation (e.g. claim no efficacy or needs MRI in exclusion zone), turn stim off for > 3 months to make sure VNS is indeed not helping.
- remove as much of the lead as possible if explanting a system (ideally, should be < 2 cm remaining to allow MRI in exclusion zone – see below >>); transect lead here:



SURGICAL TECHNIQUE – NEW VNS IMPLANTATION

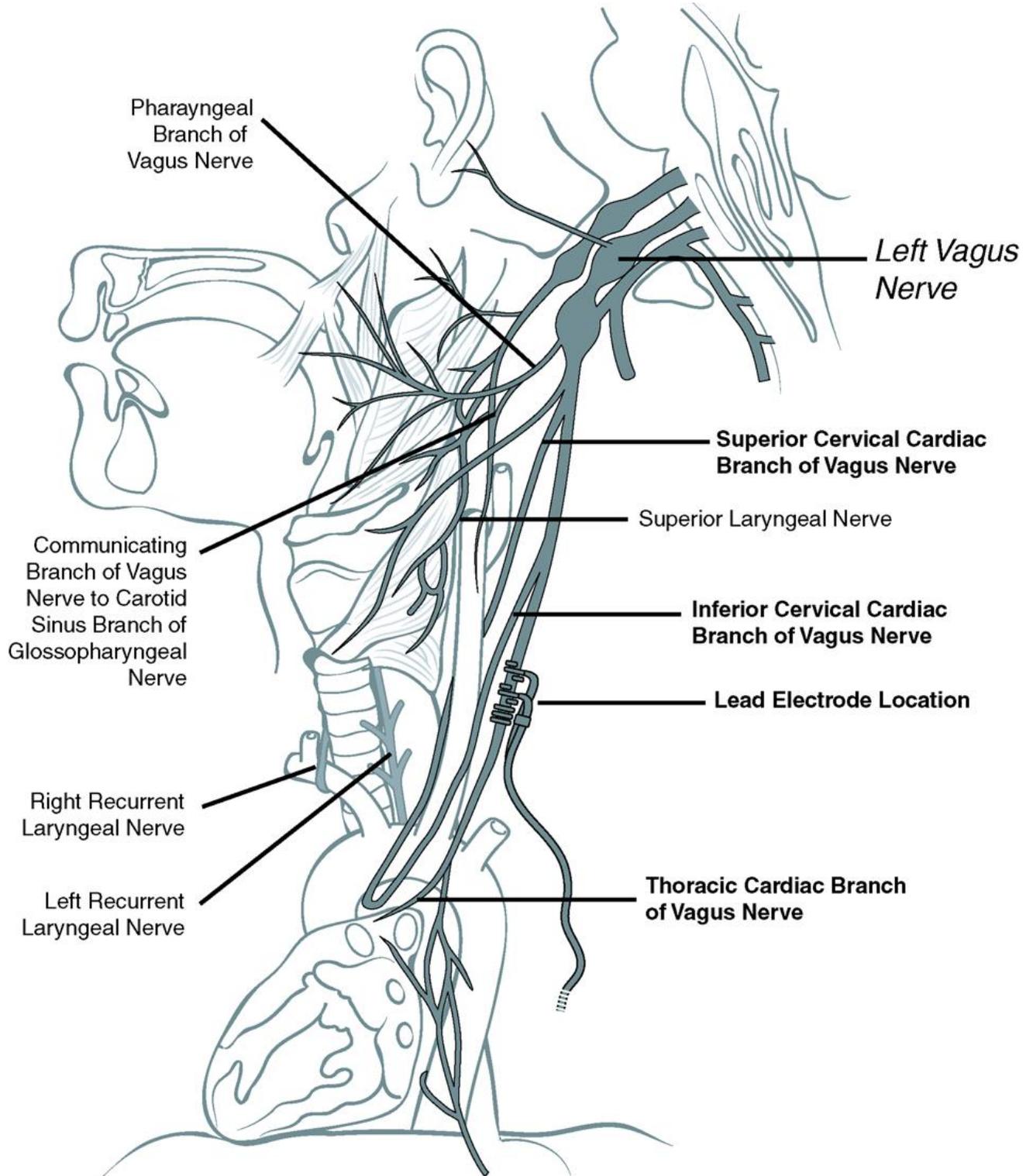
GENERAL SCHEMA





Source of picture: Livanova >>

ANATOMY



Source of picture: Livanova >>

- nerve usually lies in posterior groove between carotid artery and internal jugular vein.

POSITION

- on gel donut / towels (Dr. Holloway)

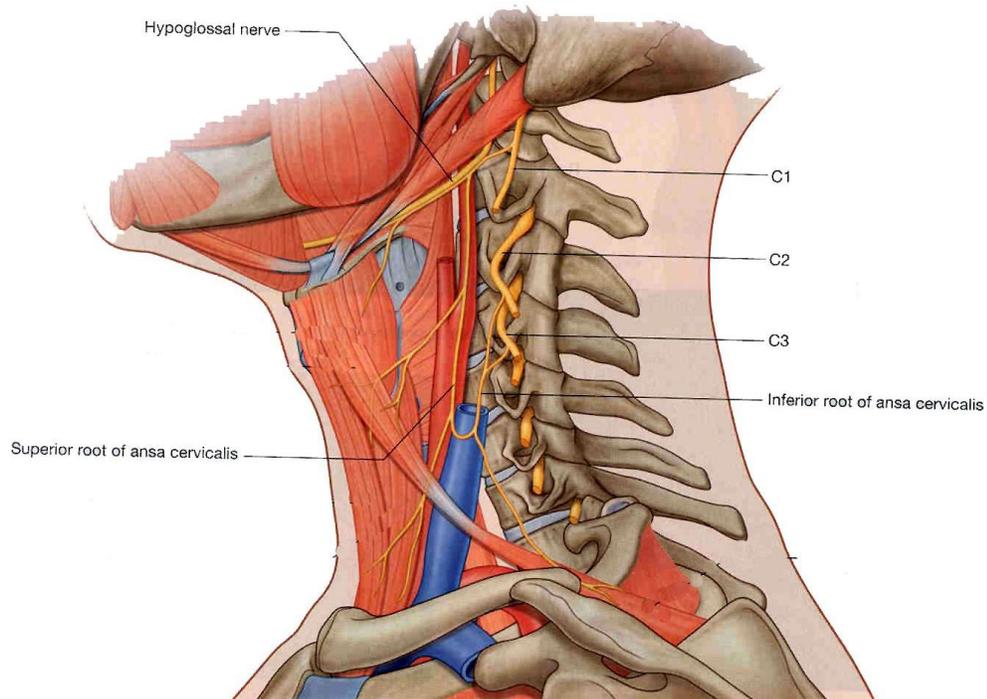
- Dr. Holloway places saline bag under neck to push viscera anteriorly.
- head:
 - a) straight (Dr. Holloway - any rotation distorts anatomy!!!)
 - b) rotate head to the right (Dr. Tye) – IJ tends to overlap vagus nerve.
- arm position depends where generator is going to be placed:
 - a) arms tucked at the sides
 - b) right arm tucked at the side while left arm abducted on the arm rest (Dr. Tye for female patients places generator on the side of the chest lateral to breast; Dr. Collins places generator at anterior axillary fold).

INCISION

- at level of cricothyroid membrane (“as for C5-6 ACDF or lower if neck allows – goal to avoid cardiac nerves”).
- inject local anesthetic with epinephrine early – allows hemostatic action to begin while sterile draping the patient (minimize electrosurgical use to occasional bipolar cautery use during dissection; should not need to use monopolar Bovie cautery at all!)

DISSECTION

- dissect “as for 3-level ACDF” – down to spine along medial edge of carotid; then dissect laterally along anterior surface of carotid until finding groove between carotid and IJ (do not dissect beneath SCM and do not expose IJ – IJ is fragile + does not need to be exposed at all!); Dr. Collins splits platysma along fibers and retracts omohyoid inferiorly using vessel loop.
- Dr. Collins leaves some adventitia (edges of carotid sheath) on carotid and IJ (to engage retractor blades).
- using right-angle dissector & Metz expose left vagus nerve half-way between clavicle and mastoid process (below where superior and inferior cervical cardiac branches separate from vagus nerve - stimulation of either of these two branches may cause bradycardia and/or asystole)
 - N.B. main vagus nerve is the largest of three nerves! (usually one may encounter a thin flat nerve - superior root of ansa cervicalis – situated anteriorly between IJ and carotid):

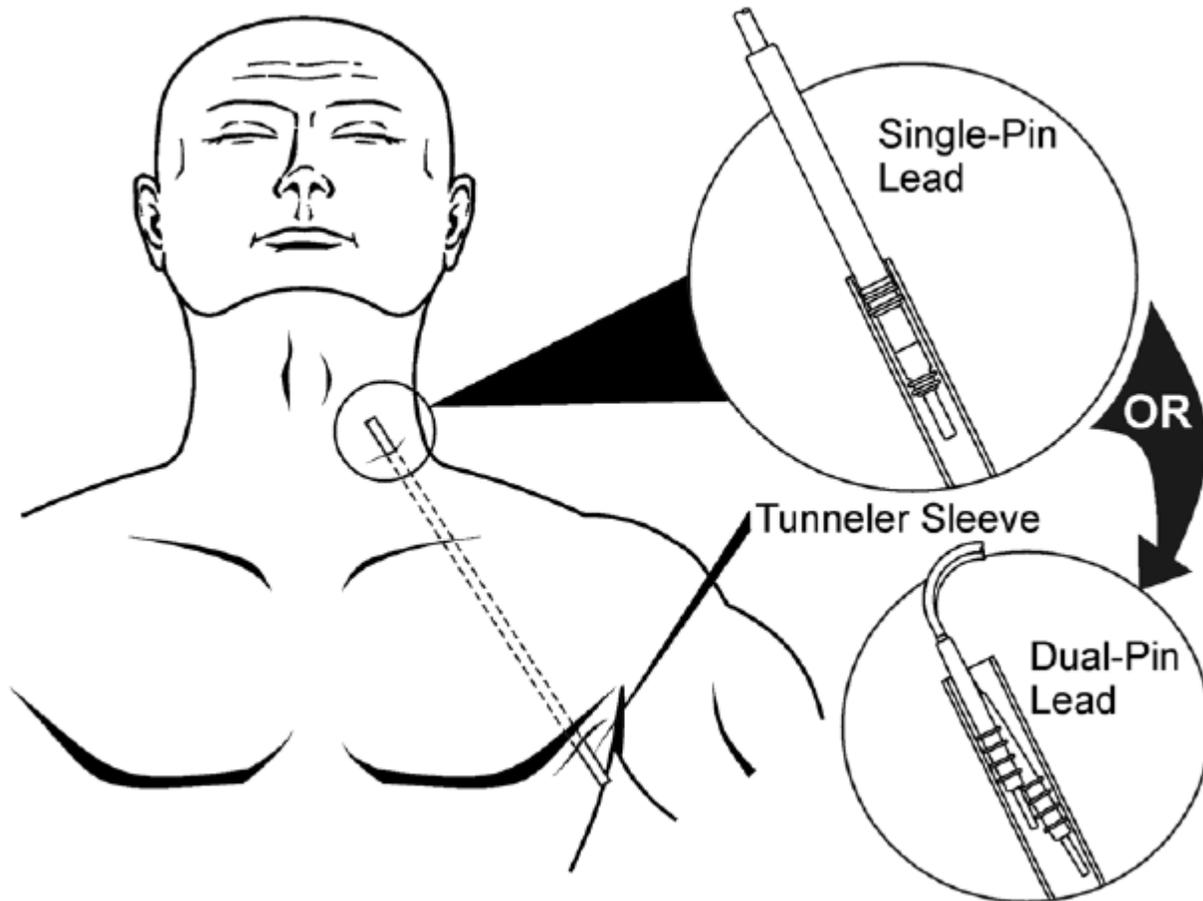


N.B. based on 50 cadaver study for vagus sympoty, in 68% of cases, left vagus is situated *anterior* to common carotid (on the right, in 64% of cases vagus is *posterior* to CCA)

- expose 3 cm of vagus nerve - facilitates placement of lead helices on nerve.
N.B. ensure perfect hemostasis – use Gelfoam with thrombin (do not use electrocautery on or near nerve!)
- stretching nerve or allowing it to dry may result in temporary swelling → constriction → vocal cord dysfunction.
- **Dr. Collins** skeletonizes nerve thoroughly – removes all epineurium to minimize impedances (to save battery) – he aims towards < 1500 ohm; risk – disturbing vasa nervorum and inducing later fibrosis.

LEAD TUNNELING

- may do before wrapping lead around nerve.
Dr. Collins uses two plastic sheaths – one inside another – pulls lead through clear large plastic tunnel (protects lead).
Dr. Collins tunnels plastic straw but not the lead itself – so when placing lead, no need to fight with lead memory and torque.
- place bullet-tip end on Tunneler and tunnel subcutaneously.
- never route lead through muscle; never suture lead to muscle.
- after bullet tip has passed from one incision to other, unscrew bullet and withdraw shaft from sleeve, leaving sleeve extended through both incisions.



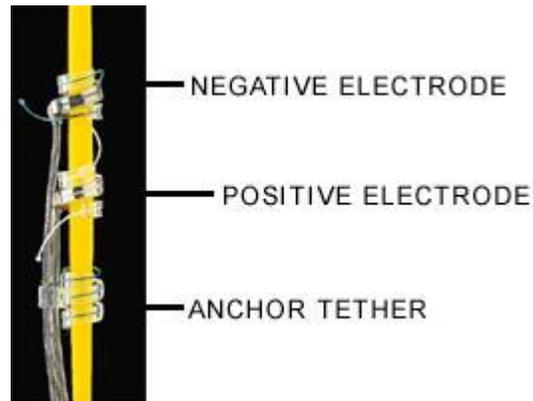
Source of picture: Livanova >>

- insert lead connector(s) inside end of sleeve at neck incision (for dual-pin lead, second connector will form slight compression fit between first lead connector tubing and sleeve inside).
- pull sleeve, along with lead connector(s), towards chest incision until lead connector(s) completely exit(s) chest incision.

WRAPPING LEAD

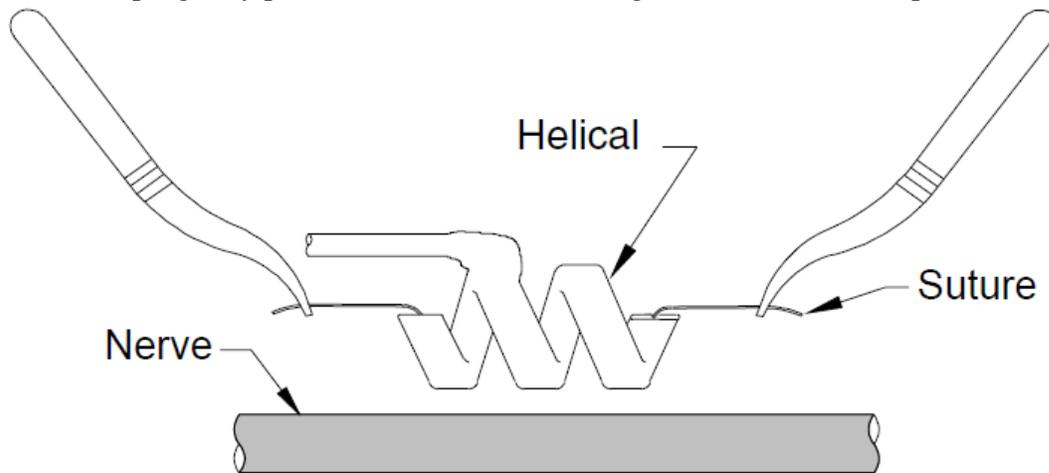
- choose **appropriately sized lead** (2.0 or 3.0 mm electrode inner diameter) - should fit snugly without constricting nerve; 2.0 mm lead should accommodate most nerves.
 - it is not possible to predict what size lead will be needed.
 - open lead from its package only when ready to implant (i.e. do not expose lead to dust or other similar particulates, because its silicone insulation can attract particulate matter).
 - do not soak lead in saline or similar solution before implanting it - may cause insulated portions of connector pin to swell and become difficult to insert into Pulse Generator.
- use soft **rubber vessel loops** to gently lift the nerve, if necessary.
 - **Dr. Collins** instead of vessel loop places small cottonoid underneath nerve.
- helical electrodes and anchor tether are coiled around nerve, beginning with electrode that is farthest from lead bifurcation (with green suture embedded in helical material); alternatively, helices can be placed by putting anchor tether on first (distal to head), next placing electrode closer to lead bifurcation (with white suture), and then placing electrode farthest from lead bifurcation (with green suture).

Minus goes cranial:

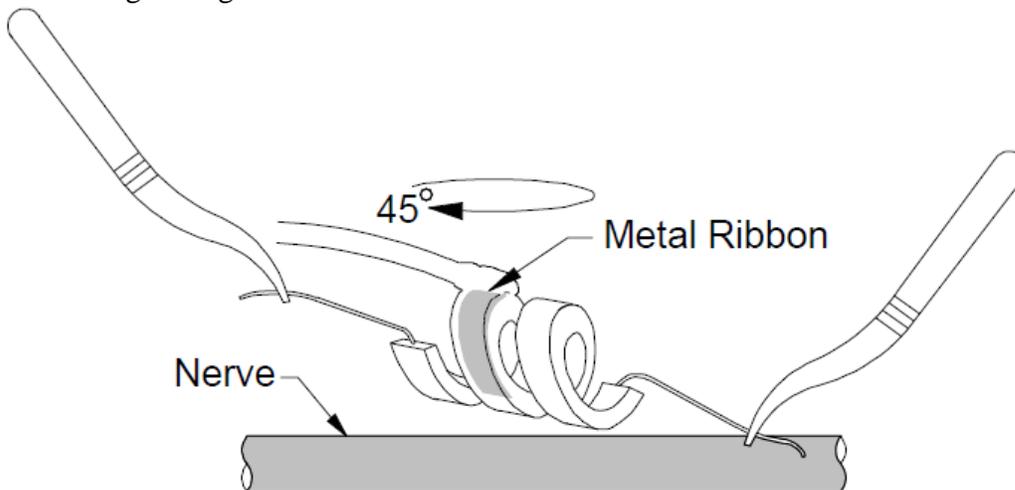


N.B. if **contacts are applied upside down**, VNS will stimulate efferent fibers – may cause **diarrhea!**

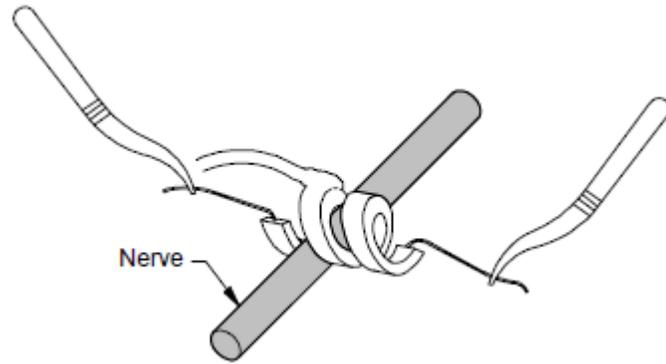
- with forceps, gently pull each end of helical, using attached sutures to spread helical.



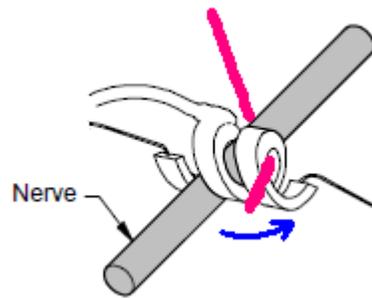
- starting with opened helical spread directly above and parallel to exposed nerve, turn helical clockwise at a 45 degree angle to nerve:



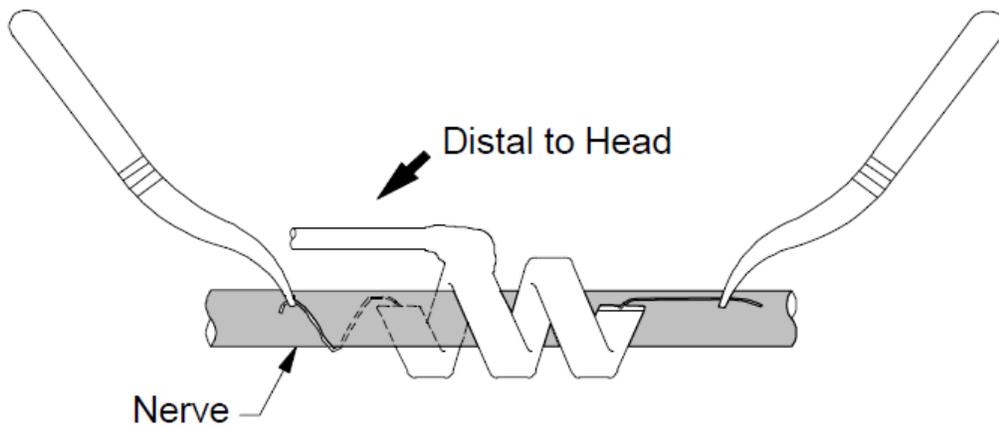
- place turn of helical where lead wire connects to helical (section with metal ribbon) onto nerve:

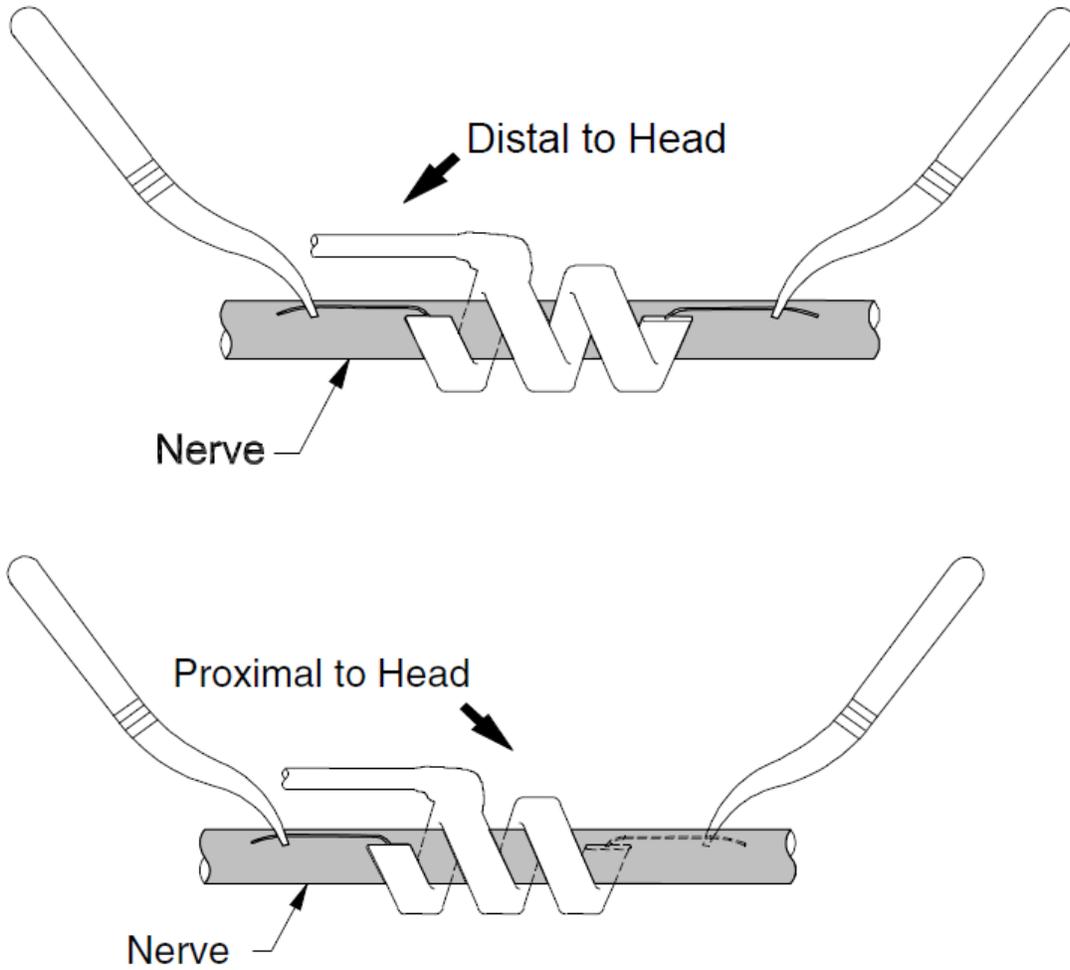


Dr. Collins uses *blunt nerve hook* to wrap (procedure can be done by one person!) – stretches pigtail so metal contact sits on nerve; releases stretch so pigtail recoils and grasps nerve; then nerve hook goes under nerve, hooks and pools one side of pigtail; repeat on the other side of pigtail:

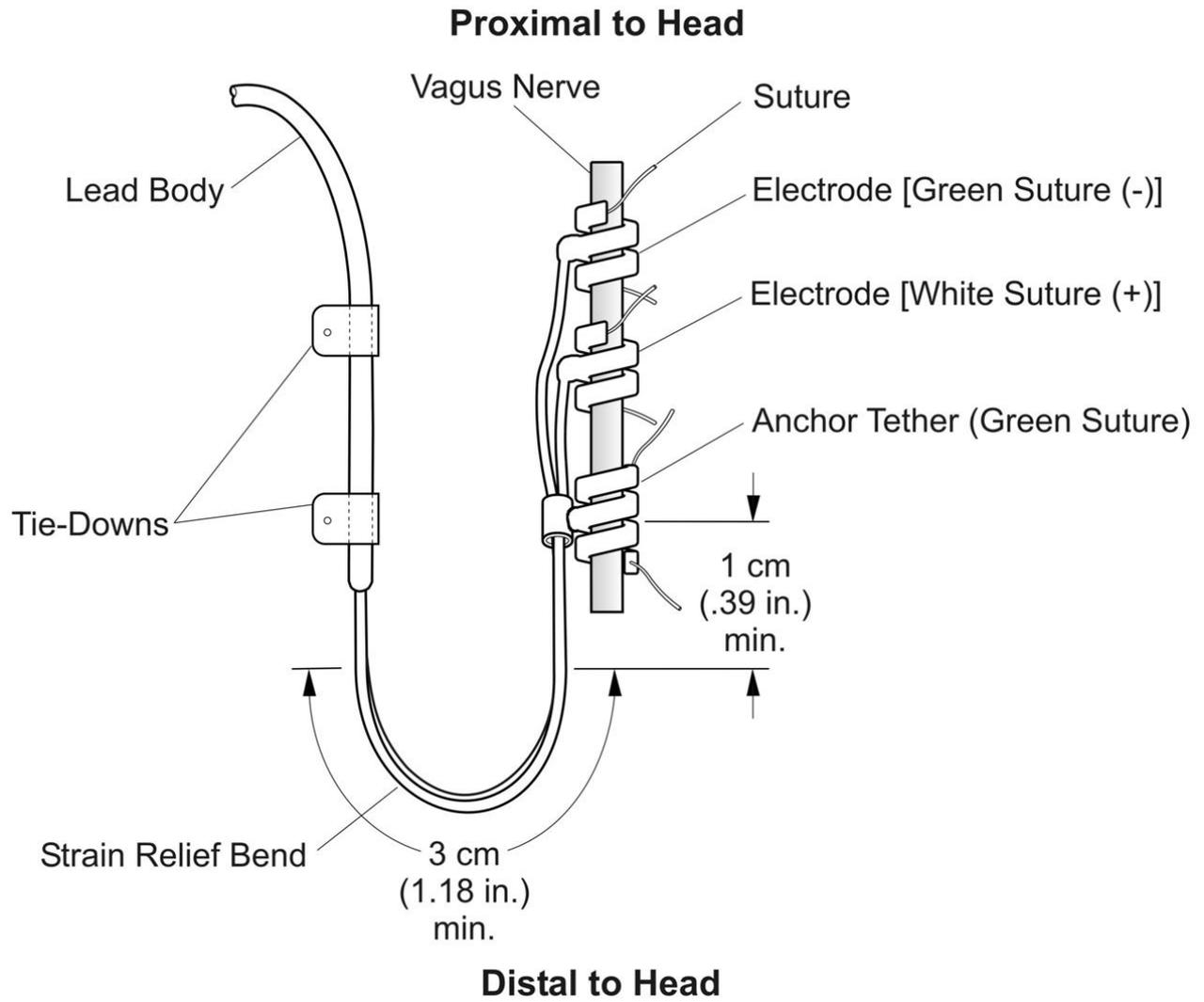


Source of picture: Viktoras Palys, MD >>

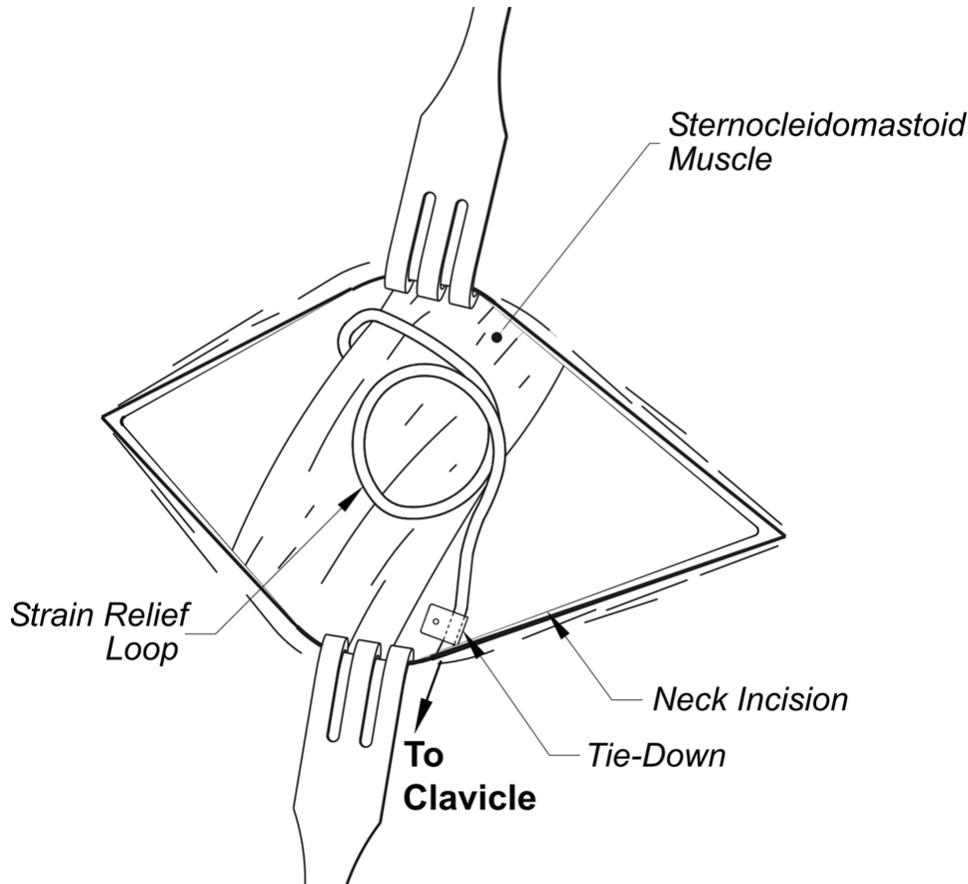




- form strain relief bend (lay it inside carotid sheath) and strain relief loop to provide adequate slack and allow for neck movement.



Proximal To Head

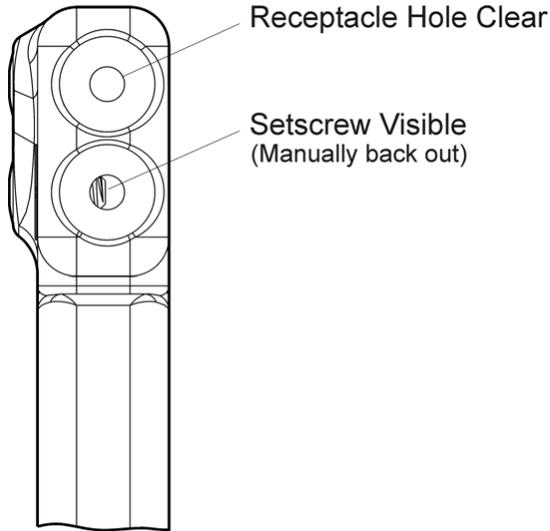


Source of pictures: Livanova >>

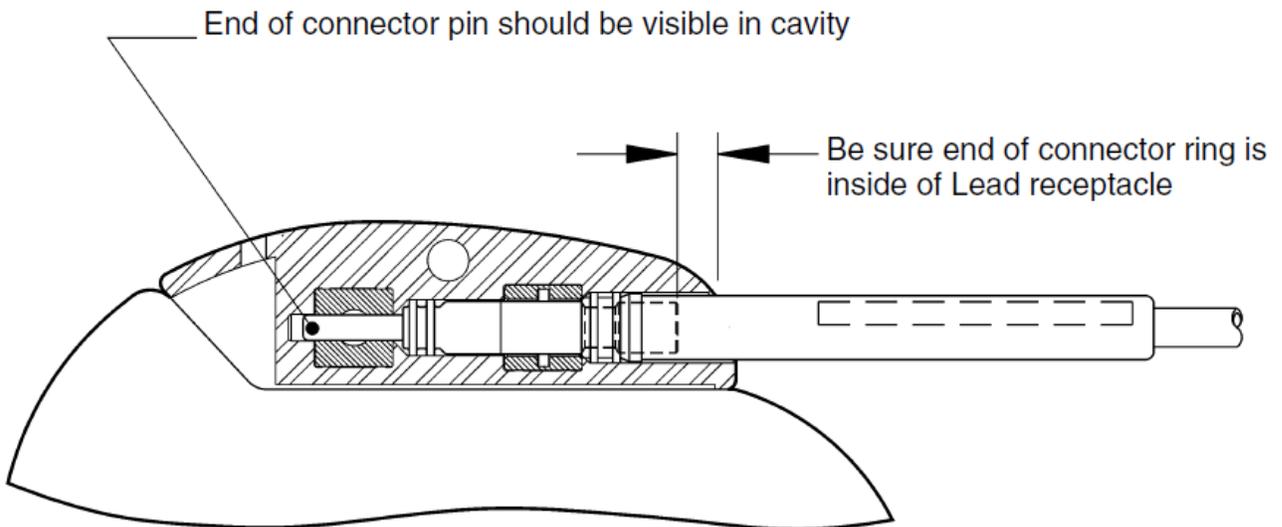
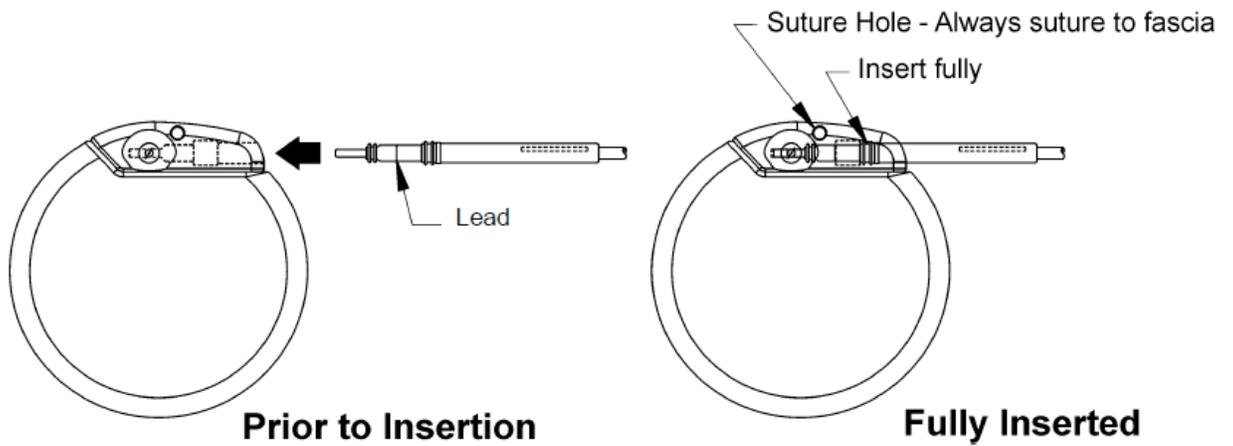
Dr. Collins never places tie-down tabs under the skin (risk of erosion!); he places tabs at least under platysma.

PULSE GENERATORS

- if patient is a twiddler, may consider implanting battery in the back.
- do not use electrosurgical equipment after Pulse Generator has been introduced to sterile field - exposure to this equipment may damage Pulse Generator.
- Pulse Generator is implanted just below clavicle in subcutaneous pocket in the left upper chest along axillary border.
- place extra coiled lead to side of Pulse Generator, not behind it.
Do not place lead slack *under Pulse Generator*, because doing so could result in insulation failure and system malfunction.
- back out setscrew(s) and insert lead:



- it is ok to implant battery upside down.
- note for dual pin leads (now obsolete) - reversal of lead polarity has been associated with increased chance of bradycardia in animal studies.



- if patient has experienced **asystole**, **severe bradycardia (heart rate < 40 bpm)**, or clinically significant **change in heart rate** during System Diagnostics (lead test) at time of initial device implantation, patient should be placed on cardiac monitor during initiation of stimulation.

models 100-102R, the test will stimulate at **1 mA** for **45 seconds**.

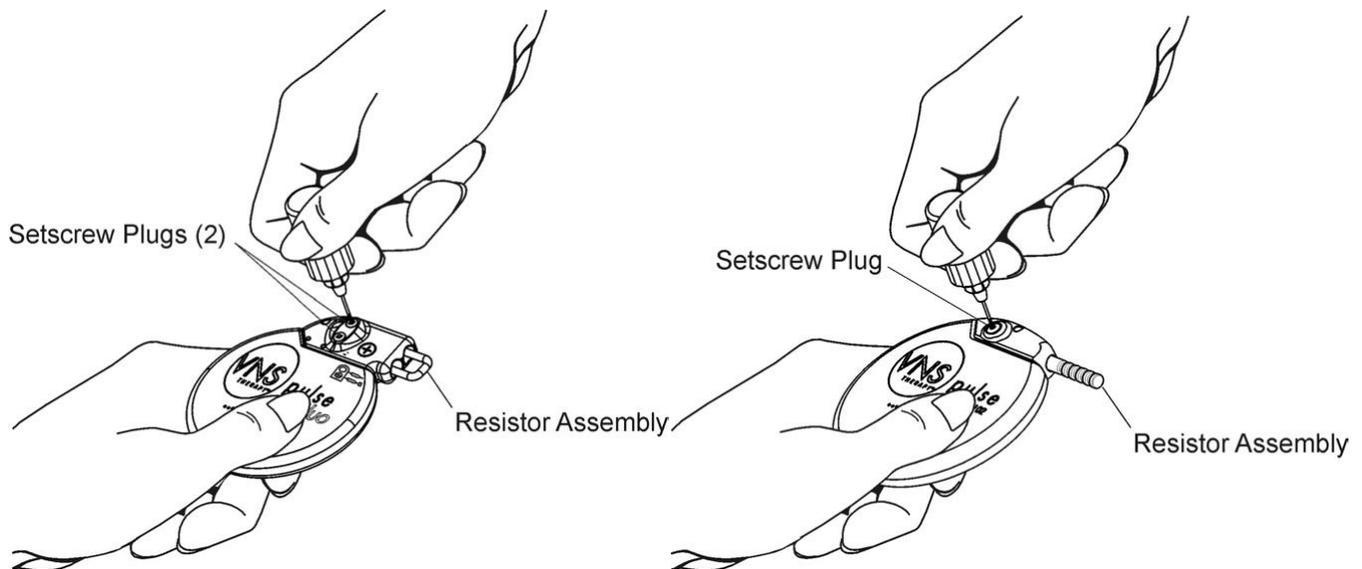
models ≥ 103, the test takes approximately **5 seconds**; **1 mA** output current will be used when the device is set to 0 mA; otherwise, it will use **the programmed output current** (e.g. 0.75 mA for 5 seconds if programmed at 0.75 mA, or 2.5 mA for 5 seconds if programmed at 2.5 mA).

N.B. **have screw ready!!!** – if patient goes into severe bradycardia, may quickly disconnect lead (as stimulator goes into testing cycle and won't be easily stopped)

- two types of tests (interrogation):

System Diagnostics – if it fails (lead impedance “HIGH” or “LOW”) → **Generator Diagnostics** (test performed with test resistor that is included in Pulse Generator packaging or use accessory kit #502) - this test will verify that Pulse Generator is functioning properly, independent of lead.

N.B. **IPG does not need to be in a pocket** – impedances are checked between lead contacts (vs. in DBS, impedances are also checked between a contact and IPG case – so called “monopolar configuration”).



Source of picture: Livanova >>

- when implanting ≥ 106 model - make sure it **senses heart rate** (**IPG has to be in a pocket** to test this).

INTRAOPERATIVE PROGRAMMING

- see below >>

CLOSURE

- all wounds are copiously irrigated with bacitracin solution and filled with 1 gram of vancomycin powder.
- secure IPG by placing braided nonabsorbable suture (e.g. 2-0 silk) through suture hole and attaching it to underlying pectoralis fascia (not to muscle).
N.B. battery has only one hole for anchoring!
- deep interrupted absorbable (e.g. 2-0 Vicryl) stitches are placed to approximate the bulk of soft tissue (adipose tissue in the chest, platysma muscle in the neck).
- skin edges are sutured with interrupted inverted (deep dermal) stitches using thinner absorbable sutures (e.g. 3-0 Vicryl).
- if there is an increased risk of skin dehiscence, place additional simple running absorbable monofilament suture (e.g. 4-0 Monocryl) on epidermis for extra reinforcement.
- skin adhesive (e.g. Dermabond) is applied; once this had completely (!) dried, a sterile dressing (e.g. Tegaderm) is applied.

POSTOPERATIVELY

- old school was not to program Pulse Generator to stimulation treatment for at least 14 days after initial implantation; now we **start stim at lowest settings (0.25 mA) in OR.**
- rarely, *neck brace* can be used for first week to help ensure proper lead stabilization.

PATIENT INSTRUCTIONS

At least 6 hours of **observation** in a hospital after surgery.

Bathing: you can take shower anytime. No bath tub or soaking of incision for 6 weeks.

Dressing: remove plastic clear dressing (e.g. Tegaderm) at 3 days after surgery:



Source of picture: Viktoras Palys, MD >>

skin glue will stay on and will flake off on its own in a few weeks.

Regimen: for 6 weeks perform gentle neck range of motion exercises.

If, at any time, you notice signs of infection (worsening pain, redness, swelling, drainage), please contact the surgeon's office ASAP.

MRI

Full instructions >>

Check vnstherapy.com/healthcare-professionals/mri – really easy to use website to find recommendations for your device!

- **compatible with 1.5-3.0 T MRI** (DBS is also approved for 3.0 T; RNS approved for 1.5 T).

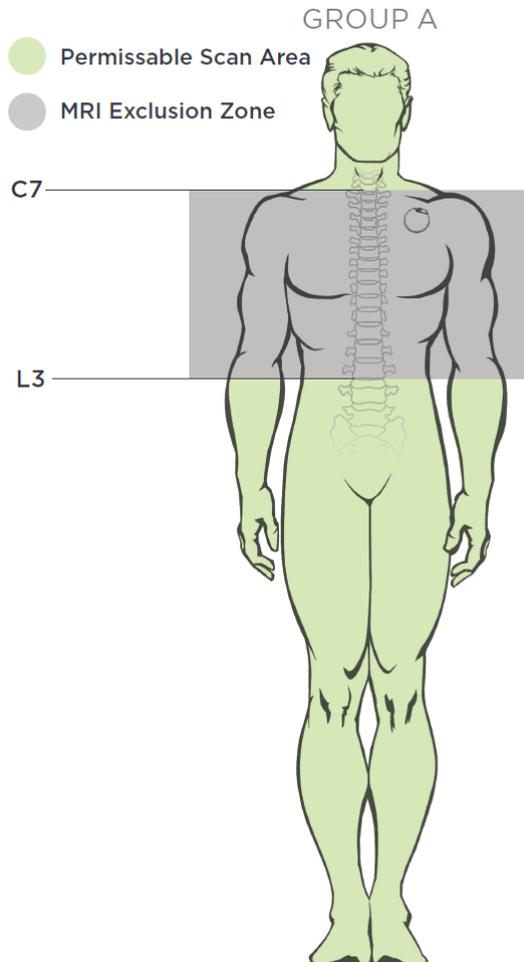
GROUP A - 103, 105, 106, 1000 IMPLANTED HIGHER THAN 4TH RIB (ARMPIT LEVEL)

No special MRI equipment/coils required

Note: The scan iso-center must be outside the exclusion zone

† Patients with implants in other locations must follow Group B scan conditions

Performing MRI with a body coil is safe when the specified conditions are followed



 MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Scanner Type	Horizontal field, cylindrical closed-bore 1.5T or 3T scanner
Operating Mode	Normal Operating Mode
Exclusion Zone	Body coil: C7-L3 Transmit-receive head or extremity coil: C7-T8
Max Spatial Gradient	≤3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	Transmit: Body coil or Transmit-receive head or extremity coils Receive: No Restrictions
Max SAR	Transmit head coil: 3.2 W/kg Transmit body coil: 2.0 W/kg
System Programming	Stimulation OFF Sensing OFF* *for select models with AutoStim mode Optional device features OFF (Model 1000 only)
Exposure Time	Transmit head or extremity coil: No restrictions Transmit body coil: ≤ 15 minutes of active scan time within a 30 minute window
Additional Restrictions	Transmit head or extremity coil: none Transmit body coil: Circularized Polarized mode only

- OK to use **transmit body coil** (15 min scan, 15 min break time) and **3T MRI**.
- if the patient requires a MRI of the **C7-T8 area using a head/extremity coil** or **C7-L3 area using a body coil**, surgical removal of the VNS is required.

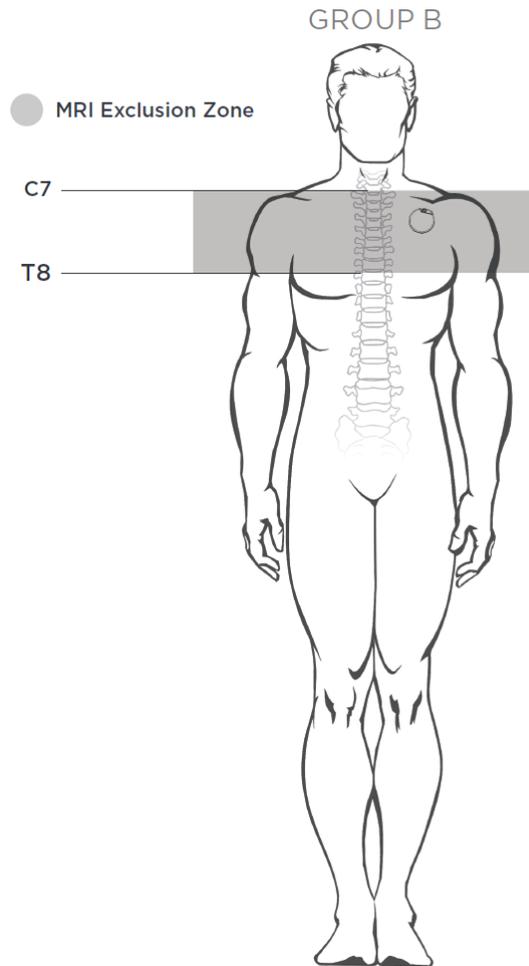
GROUP B – 102, 104, also Group A implanted below 4th rib

Requires local transmit-receive coil

Availability may vary

Permissible scans include head, knee, ankle, and wrist

Performing MRI with a local transmit/receive coil is safe when the specified conditions are followed



 MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Scanner Type	Horizontal field, cylindrical closed-bore 1.5T or 3T scanner
Operating Mode	Normal Operating Mode
Exclusion Zone	C7-T8
Max Spatial Gradient	≤3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	Transmit-receive head or extremity coils
Max SAR	Transmit-receive head coil: 3.2 W/kg
System Programming	Stimulation OFF Sensing OFF* *for select models with AutoStim mode Optional device features OFF (Model 1000 only)
Exposure Time	Transmit-receive head or extremity coil: No restrictions
Additional Restrictions	None

- surgical removal of the VNS is required if MRI using a **transmit RF body coil** is needed.
- not all head RF coils are transmit and receive type; many are receive only; use of any local receive coil with the body coil in RF transmit mode presents the same RF heating hazards as the body coil alone with no local coils.

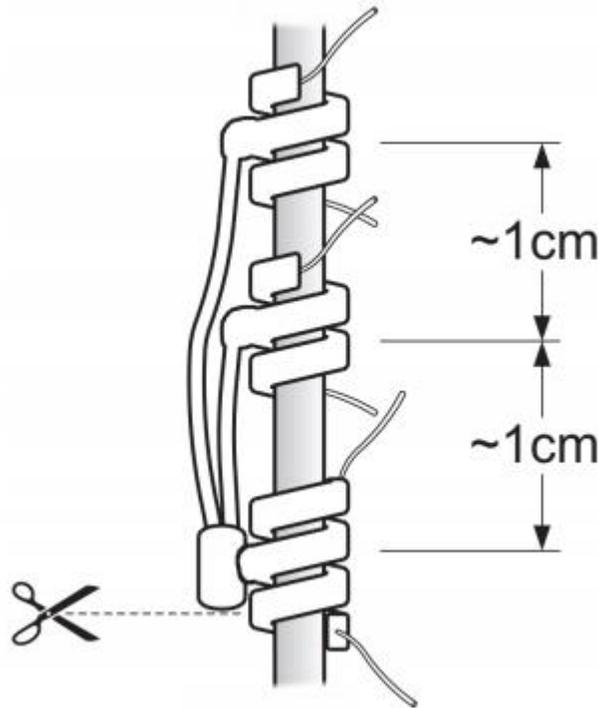
CUT / BROKEN LEAD

	<p>Suspected Lead Break</p>  <p>OR</p> <p>Lead only >2 cm remaining</p> 	<p>Lead only ≤ 2 cm remaining*</p> 
Exclusion Zone	C7-T8	None
 MR Conditional	Yes	Yes
Static Magnet Strength	1.5T or 3T	1.5T or 3T
Operating Mode	Normal Operating Mode	Normal Operating Mode
Max Spatial Gradient	≤3000 Gauss/cm	≤3000 Gauss/cm
Max Slew Rate	200 T/m/s	200 T/m/s
RF Coil	Transmit-Receive head or extremity coils only	Transmit: Body or transmit-receive head or extremity coils Receive: No Restrictions
Max SAR	Transmit/receive head coil: 3.2 W/kg	Transmit head coil: 3.2 W/kg Transmit body coil: 2.0 W/kg

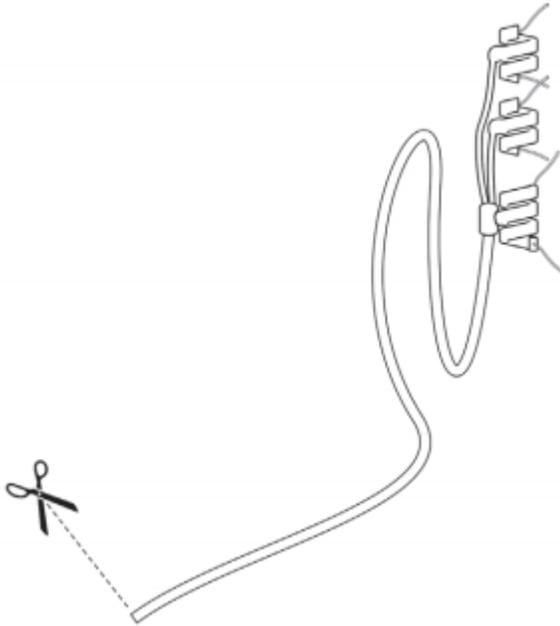
*Equivalent to clipping the lead at the anchor tether

- **safe length of lead segment remaining (i.e., ≤ 2 cm)** can be assessed by taking an x-ray. The length of 2 cm can be approximated by visualizing the distance between the positive and negative electrode (~1 cm). By design, there is approximately 1 cm between the positive electrode and the anchor tether, which is also likely remaining. Surgeons are instructed to remove as much of the lead as possible if explanting a system.

- length of lead segment remaining (i.e. ≤ 2 cm): MRI using the **body coil**, or MRI of the head or extremities with a **head coil or local (extremity) coil** (respectively) is allowed if the lead is transected here:



- if the lead is transected > 2 cm, only a transmit/receive **head MRI** or transmit/ receive **extremity MRI** is recommended; **full body MRI** is not allowed.



Warning: If it appears that > 2 cm of lead remains, then the patient cannot have an MRI with the body coil, but can still have an MRI using a extremity transmit/receive or head transmit/receive coil. Abandoned lead wires present increased risk of thermal injury to patients during MRI procedures based on their length and their exposure to RF.

DEVICE PREPARATION FOR MRI SCAN

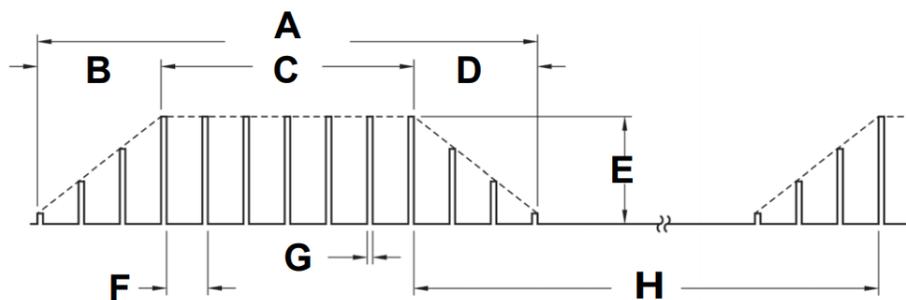
1. **Perform an interrogation and record** the information in the patient record (this information is used to restore the device settings after the MRI or in the rare case of a reset):
2. **Program** the parameter settings as follows (VNS needs to be **turned off** by programmer, not by magnet):
 - Normal Output Current: 0 mA
 - Magnet Current: 0 mA
 - Model 106 and 1000 only:
 - Detection "OFF"
 - AutoStim Output Current: 0 mA
 - Turn off any other optional device features (Model 1000 only).

N.B. practical advice – **only need to turn magnet to 0 mA** (all other parameters can be left unchanged)

3. **Verify** that placement of VNS is **located between C7-T8**.
Caution: MRI with a VNS implanted outside C7-T8 has not been evaluated!

ELECTROSURGERY

OK to use Bovie if far from VNS.

PROGRAMMING

- A** Stimulation Time
- B** Ramp Up (2 sec.)
- C** On Time
- D** Ramp Down (2 sec.)
- E** Output Current
- F** 1/Signal Frequency
- G** Pulse Width
- H** Off Time

Intraoperative, right after VNS implantation (e.g. in OR):

1. **Interrogate** generator

2. Perform **System Diagnostics** (system stimulates at 1 mA or set output current – watch for heart rate change)
3. **Program – normal mode:**
 - output current 0.25-0.5 mA
 - frequency 20-30 Hz
 - pulse width 250 msec
 - 250 msec - all axons get excited (default is 500 msec but that increases side effects, e.g. sleep apnea, and drains battery)
 - on time 30 seconds, off time 5 minutes
4. **Program – magnet mode:** current 0.25 mA higher than output, 250 msec pulse width for 30 seconds
5. **Program – AutoStim mode:**
 - Verify Heartbeat Detection (check is device detected HR and pulse ox HR match)
 - heart rate threshold 50%
 - current 0.125 mA higher than normal output
 - stim time 30 secs
6. Always **Interrogate** generator again as last step in session to verify settings

N.B. only increase *current* from factory 0 mA to 0.25-0.5 mA; for the rest – may leave factory defaults.

MAGNET MODE

- patient (or caregiver) can use magnet (e.g. in bracelet) to give additional boost stimulation PRN (program **0.25 mA** higher than regular mode with 250-500 msec pulse width for 30* seconds).
 - *default is 60 secs but in studies seizures stop within 10 seconds, thus, 30 seconds is plenty.
- if seizures are successfully aborted with magnet, increase regular mode current to the one that magnet uses.
- if magnet is held over device for > 3 seconds, device is turned off and stays off as long as magnet is held on (sometimes patients make shirt pocket to hold magnet to keep magnet on and VNS off – marathon runners so VNS does not interfere with breathing; singers – so voice does not change).

AUTOSTIM – TACHYCARDIA DETECTION

82% of patients have ictal tachycardia (if epilepsy involves autonomic centers; cf. frontal lobe epilepsy usually has no tachycardia) – candidates for AutoStim.

AutoStim - detects and responds to heart rate increases that may be associated with seizures (closed-loop system)

N.B. just **sensing heart rate** consumes approx. 20% (2 years) of battery life!

- AutoStim monitors **the last 5 mins of heart rate** to have baseline rate.
- AutoStim triggers if **heart rate increases from baseline to threshold over 10 seconds** (vs. during physical exercises, heart rate increases slower).
- why not to use just AutoStim and avoid chronic stimulation (thus saving battery):
 - longterm benefits (seizure control, depression treatment) depend on chronic stimulation.
 - vagus nerve is not used to receive stimulation, so AutoStim causes “shock” sensation.

Ictal tachycardia

- true ictal tachycardia (> 100 bpm with at least 55% increase or 35 bpm increase from baseline) is observed in 16%-17% of seizures; when using a more liberal threshold of $\geq 20\%$ increase in heart rate, up to 66% of seizures could be detected but at the cost of 7 false detections per hour.

Programming

- **Threshold for AutoStim:** set initial heart rate threshold 50% (setting range is from 20% to 70%. 20% is most sensitive. 70% is least sensitive)
- **Heartbeat Detection (Sensitivity)** ranging from 1 to 5, with “1” being the least sensitive and “5” being the most sensitive setting.
N.B. model 106 is only capable of detecting heart beats in the range 32-240 bpm (vs. model 1000 - 28-180 bpm)
- program **0.125 mA** higher than regular mode (i.e. in the middle between chronic stim and magnet mode) for 30* seconds.
*in studies, seizures stop within 10 seconds, thus, 30 seconds is plenty, plus, resets heart rate calculator sooner (vs. if stim was for 60 secs).
- to have AutoStim enabled, off periods have to be > 0.8 min.

The multicenter European Cardiac Based Seizure Detection Trial (E-36) - tested a heart rate-triggered VNS device in 30 patients with frequent seizures and well-established drug-resistant epilepsy that was not amenable to epilepsy surgery. They were also chosen on the basis of frequent tachycardia, the feature that the device was designed to detect.

BRADYCARDIA DETECTION – “SUDEP MONITOR”

- enabled only for 7.5 mins after magnet swipe or AutoStim (i.e. VNS monitors if patient goes into bradycardia during or after seizure – SUDEP risk).

IMPEDANCE

- cannot test impedances preop if battery is dead (but starting with model 103, battery retains charge for lead testing).
- VNS does not have external extension leads to test impedance intraop if battery is dead.
- normal impedances are $< 2000-4000$.
- **high lead impedance** is defined as ≥ 5300 Ohms, however, there is no upper limit where IPG will stop delivering therapy (all depends on settings; if impedance > 10 kOhm, likely there is very little therapy being delivered)
- **low lead impedance** is defined as ≤ 600 Ohms.

DUTY CYCLE

- stimulation (on time) as a percent of the whole time.
- no studies on how many hrs/day are needed to achieve neuromodulatory effect (based on animal studies, 100% [i.e. continuous stim] would be the best but depletes battery fast).

Programming Phase I

aka "1 tab BID → 2 tab BID"

- gradually increase of **output current** - stepwise, **every 2 weeks***, up to 2.5 mA** (as long as patient is seeing improvement; when plateaus, go one step back and start phase II).
 - *can be done **every 15 mins** in clinic if patient tolerates **side effects**
 - **1.5 mA should activate all axons so no real need to go beyond that (all further efficacy depends on duty cycle) but there are patients that benefit from 3.5 mA.
- if VNS is implanted for emergency cases (patient in status), current may be ramped up quickly.

Programming Phase II

aka "2 tab BID → 2 tab TID"

- increasing **duty cycle** **every 3 months**.
- side effects do not get worse** during phase II.

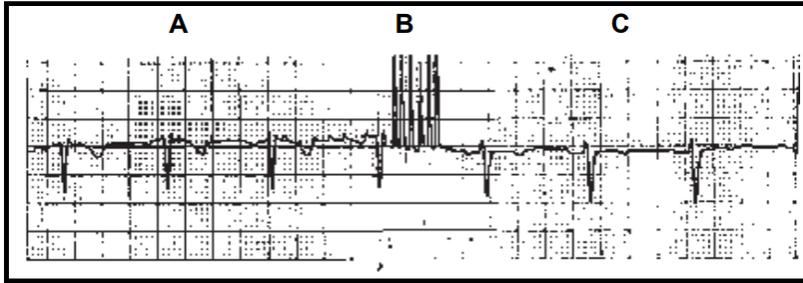
		OFF Time (min)							
		0.2	0.3	0.5	0.8	1.1	1.8	3	5
ON Time (sec)	Duty Cycles* (% ON Time)								
	7	58	44	30	20	15	10	6	4
14	69	56	41	29	23	15	9	6	3
21	76	64	49	36	29	19	12	8	4
30	81	71	57	44	35	25	16	10	5
60	89	82	71	59	51	38	27	18	10

duty cycles in gray are not recommended as they represent parameter combinations with ON > OFF time

SIDE EFFECTS

- hoarseness** or **change in voice** (30-50%)
 - cough**, paresthesia, pain, dyspnea, or headache
 - sleep apnea** (in adults, esp. if 500 msec pulse width is used).
 - Significant risk of de-novo or aggravating **sleep breathing disorders** in up to 57% of patients!
 - asystole** (reports of occurring > 1 year after VNS surgery)
- there are no long term side effects of chronic stimulation (reported change in axon diameter but no physiologic effects)

Generator data communication produces an ECG artifact:



A Generator Off

B Programming

C Generator On

COMPLICATIONS

- **infection** (3-4%)
- excessive stimulation has resulted in **degenerative nerve damage** in laboratory animals, esp. when ON time exceeds OFF time (duty cycle > 50%), which can be produced by continuous or frequent magnet activation (> 8 hours).

OUTCOMES - DEPRESSION

- 1-year response rate 30-53% (vs. 10% with best non-VNS therapies).
- from an FDA-mandated registry (Aaronson, 795 patients with TRD and 5-year follow-up): **VNS plus treatment as usual** vs. treatment as usual had higher cumulative response rates (68% vs 41%) and remission rates (43% vs 26%).

OUTCOMES - EPILEPSY

- because of its lower risk for neurologic injury – VNS is standard by which all other more invasive therapies must be judged.
- long-term stimulation (> 6 months) → greater rather than lesser effect, i.e. VNS has improved efficacy over time!!!
- 50% reduction in seizure frequency in 60% of patients after 2 years of therapy (76% at 8 years)
N.B. seizure **intensity** or **duration** does not change significantly!?
- up to **8% patients** become **seizure free**.
- **25% of patients** with long-term f/u **have no benefit!**?
- it remains unclear if VNS allows to decrease AEDs.
- at 12 months, VNS improves **quality of life** by 4.5-fold (PULSE study 2014).

Example of consult:

“VNS therapy has a 60% chance of a 50% reduction in seizures and low risks of complications, but they do include infection (3-4%), hoarseness (up to 50%), neck hematoma, cardiac arrhythmia, even coma and death. It would not cure the epilepsy, thus, VNS is not indicated if the patient’s sole goal is to eliminate seizures and start driving. During appointment approximately 2 weeks after the surgery, the device will be activated but further programming will be done by epileptologist.”

Outcomes by VNS Registry + Meta-analysis

VNS therapy Patient Outcome **Registry** (5554 patients) + systematic **review** of the literature (2869 patients across 78 studies)

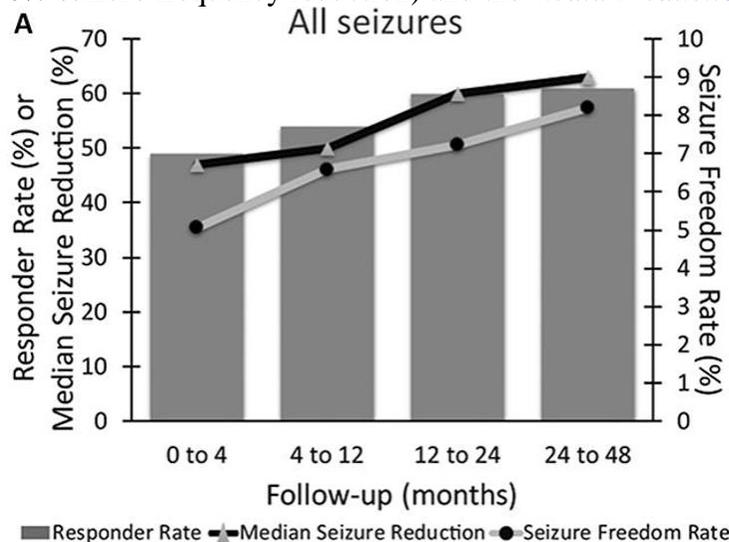
Englot et al. "Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy" Neurosurgery: September 2016 - Volume 79 - Issue 3 - p 345-353

Duration	responder rate – VNS registry% (review%)	seizure freedom (Engel Ia) – VNS registry% (review%)
0-4 mo	49% (40%)	5.1% (2.6%)
24-48 mo	63% (60.1%)	8.2% (8%)

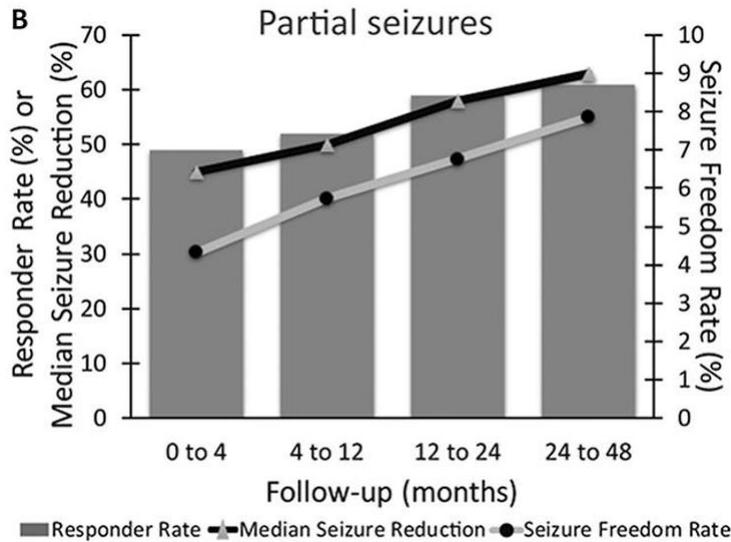
- on multivariate analysis, seizure freedom was predicted by **age of epilepsy onset >12 years** (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.38-2.58), and predominantly **generalized seizure type** (OR, 1.36; 95% CI, 1.01-1.82), while overall response to VNS was predicted by **nonlesional epilepsy** (OR, 1.38; 95% CI, 1.06-1.81).

VNS therapy **registry**:

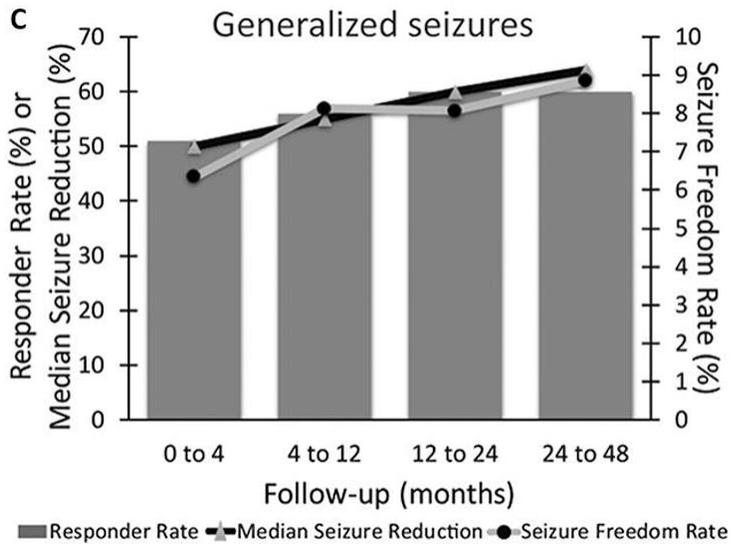
A. **All patients** - progressive increase in **seizure freedom**, paralleling increases in the rate of **response to therapy** ($\geq 50\%$ seizure frequency reduction) and the **median reduction of seizure** frequency:



B. **Partial** seizures:

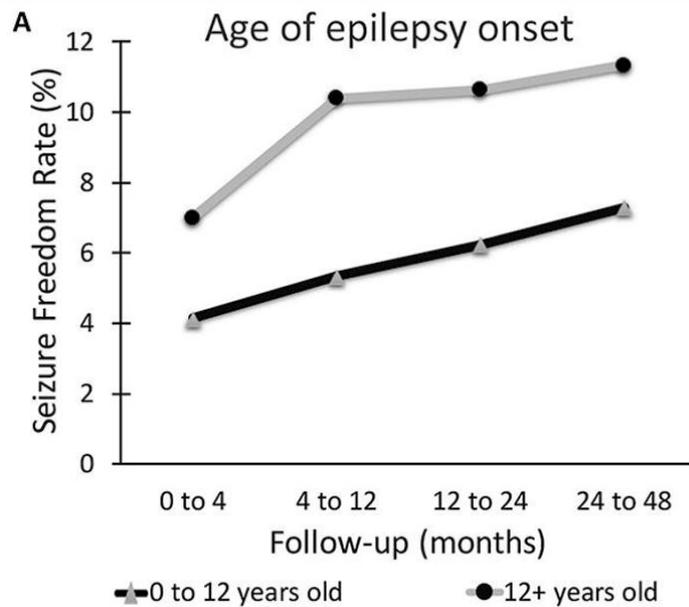


C. **Generalized** seizures:

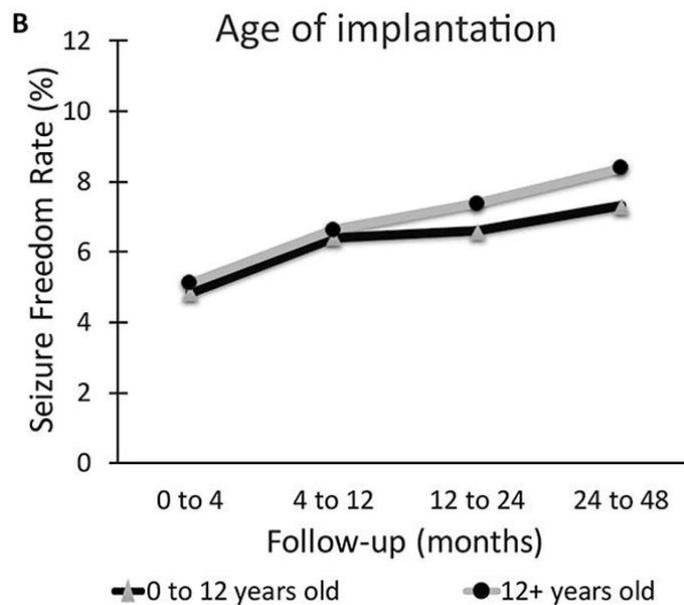


- *seizure freedom* was significantly more likely in generalized seizures at 0 to 4 months ($P < .01$, Pearson χ^2) and at 4 to 12 months of follow-up, although this difference was not significant at 12 to 24 months or 24 to 48 months ($P > .5$).
- *responder rate* and *median seizure reduction* did not differ significantly between patients with primarily partial vs generalized seizures.

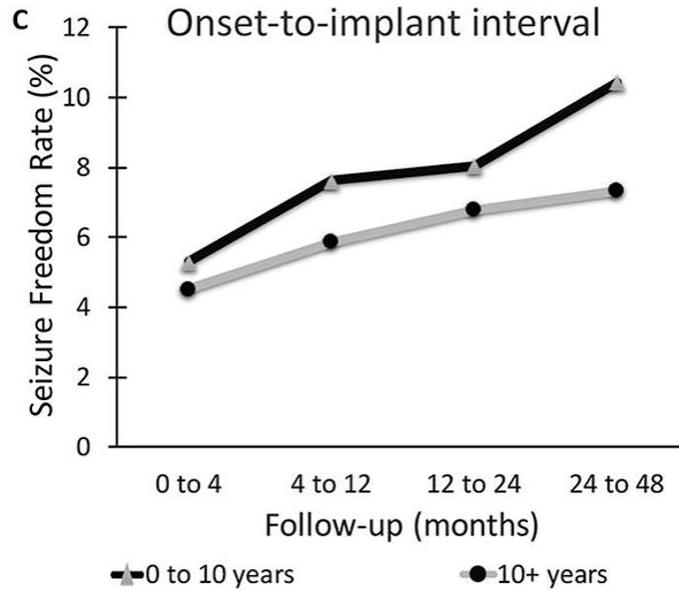
Seizure freedom rates by **age of epilepsy onset** – *older-age onset* patients do better:



Seizure freedom rates by **age of implantation** - *no significant difference* in age of implantation was observed between patients with or without seizure freedom ($P > .2$ at each time point, Wilcoxon sum rank test):



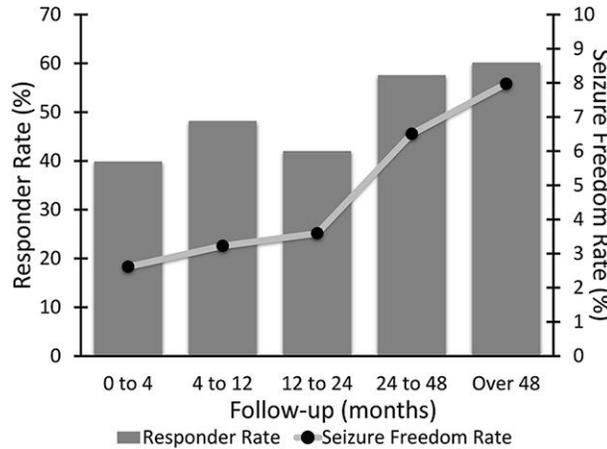
Seizure freedom rates by **onset-to-implant interval** - patients who achieved seizure freedom showed *shorter onset-to-implant intervals* than those with persistent seizures, but this difference was not significant (P range 0.07-0.26 at each time point, Wilcoxon sum rank test):



Systematic literature review:

Progressive increase in both seizure freedom and response rate over time, resembling findings from the registry.

- at latest follow-up, 60% of patients responded to VNS ($\geq 50\%$ reduction in seizures), and 8% were seizure free:

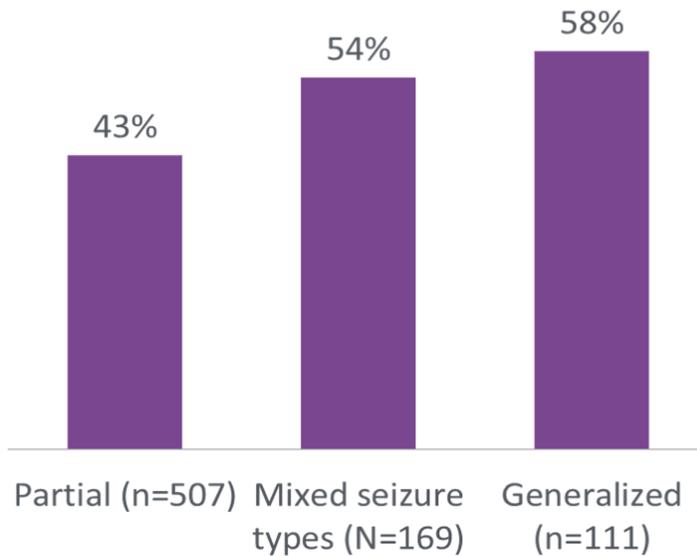


DIFFERENT EPILEPSY TYPES

Meta-analysis suggests VNS is more effective in generalized seizures than partial seizures:

Englot et al., J Neurosurg Dec 2011

Decrease in seizure frequency with VNS by seizure type



GENERALIZED EPILEPSY

Study	Response	Follow up
Labar (E04)	11/24 (45.8%)	3 mo
Holmes (U Wash)	7/16 (43.8%)	12-21 mo
Ng (Mt Sinai)	14/27 (51.9%)	Av 21.6 mo
Kostov (Oslo)	20/30 (66.7%)	Av 52 mo (17-123)

Symptomatic epilepsy

- Tonic clonic N=14 -33%
- Atypical absence N=8 -48%
- Tonic N=4 -70%
- Myoclonic N=3 -80%

Idiopathic epilepsy

- Tonic clonic N=4 -76%
- Typical absence N=4 -81%
- Myoclonic N=3 0%

Labar, D et al. *Vagus nerve stimulation for medication-resistant generalized epilepsy.* Neurology. 52(7):1510-1512, April 22, 1999

HIPPOCAMPAL EPILEPSY

- Alsaadi et al (UCSF) – 6/10 pts (60%) with > 50% seizure reduction at 1 yr.
- Kuba et al (Brno, Czech) – 3/8 (37.5%) at 1 yr and 5/8 (62.5%) at 18 mo.

TUMOR-ASSOCIATED EPILEPSY

VNS in tumor associated medically intractable epilepsy

Efficacy of vagus nerve stimulation as a treatment for medically intractable epilepsy in brain tumor patients. A case-controlled study using the VNS therapy Patient Outcome Registry. Seizure - European Journal of Epilepsy — Patel KS, et al. June 17, 2013

VNS is a viable option assuming cytoreductive and other adjuvant therapies have been fully explored.

- data from the VNS therapy Patient Outcome Registry.
- 107 patients with an epilepsy etiology related to a brain tumor, responder rate of 48% at 3 months and 79% at 24 months – similar to non-oncological patients (no statistical difference in seizure reduction compared with 326 case–control patients from the registry without brain tumors)
- no significant difference in AED usage from baseline to 24 months post implant in either group.

COST-UTILITY ANALYSIS

Pediatric patients

Helmers SL, Duh MS, Guerin A, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paediat Neurol. 2012;16(5):449–458.

- retrospective analysis using Medicaid data
- **patients 1-11 years old** (N = 238):
 - *hospitalizations and ER visits* were reduced Post-VNS vs. Pre-VNS (adjusted IRR = 0.73 [95% CI: 0.61-0.88] and 0.74 [95% CI: 0.65-0.83], respectively).
 - *average total healthcare costs* were lower Post-VNS vs. Pre-VNS (\$18,437 vs. \$18,839 quarterly [adjusted p = 0.052]).
 - *lifetime QALY gain* after VNS was 5.96 years.
- **patients 12-17 years old** (N = 207):
 - *hospitalizations and status epilepticus events* were reduced Post-VNS vs. Pre-VNS (adjusted IRR = 0.43 [95% CI: 0.34-0.54] and 0.25 [95% CI: 0.16-0.39], respectively).
 - *average total healthcare costs* were lower Post-VNS vs. Pre-VNS period (\$14,546 vs. \$19,695 quarterly [adjusted p = 0.002]).
 - *lifetime QALY gain* after VNS was 4.82 years.

Model 100 VNS

Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology. 2002;59(6 suppl 4):S44–S47.

- therapy response was defined as **≥ 25% reduction in seizure frequency**.
- aim was to assess unplanned hospital costs 18 months before and 18 months after VNS implantation in 43 patients (Sahlgrenska University Hospital in Sweden) - irrespective of whether they responded to VNS therapy!
- for all patients, ICU costs were reduced from 46,875 to 0 US dollars, ER visits from 13,000 to 9,000 US dollars, and ward stays from 151,125 to 21,375 US dollars.
- total hospital costs (for all 43 patients) before VNS therapy were 211,000 US dollars and after 18 months of treatment were reduced to 30,375 US dollars = **average cost savings of ≈ 3,000 USD/year/patient in unplanned hospital costs**.

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this [LINK](#)

Viktor's NotesSM for the Neurosurgery Resident
Please visit website at www.NeurosurgeryResident.net