Vagal Nerve Stimulator (VNS)

Used sources:
Cyberonics – VNS >>

- palliative continuously intermittent electrical stimulation with chest-implanted pacemaker-like device.
- FDA approved in 1997.

INDICATIONS

1) **partial-onset** epilepsy in adults (even with anatomically defined single foci); FDA approval: “*adjunctive therapy for reducing the frequency of seizures in patients > 12 years with partial-onset seizures refractory to antiepileptic medications*”

2) mounting evidence suggests effectiveness in **generalized** epilepsy (VNS is treatment of choice for Lennox-Gastaut syndrome)

3) FDA approved 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 an additional benefit for epilepsy patients!

   • stimulation of either vagus nerve is effective, but **left nerve is always chosen** (less likely to cause cardiac effects), usually **left cervical vagus nerve**.
- Side effect – hoarseness, cough during stimulation.

**MECHANISM OF ACTION**

- Unknown
- Vast majority of vagal fibers are afferent - 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:

![Brain Diagram]

**TECHNIQUE**

GENERAL SCHEMA
Vagal Nerve Stimulator

VNS Therapy Lead

VNS Therapy Pulse Generator
ANATOMY
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”)

### DISSECTION
- dissect “as for 3-level ACDF” – down to spine along medial edge of carotid; then dissect 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)
  
  NB. main vagus nerve is the largest of three nerves! (usually on top of vagus there is “flat nerve” – thin flat nerve)
- expose 3 cm of vagus nerve - facilitates placement of helices on 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.

### LEAD TUNNELING
- 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.
• 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), from chest incision end 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.
  — 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 lift 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).
• 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:
- form strain relief band (lay it inside carotid sheath) and strain relief loop to provide adequate slack and allow for neck movement.

**Proximal to Head**

- Vagus Nerve
- Suture
- Electrode [Green Suture (-)]
- Electrode [White Suture (+)]
- Anchor Tether (Green Suture)

**Distal to Head**

- Lead Body
- Tie-Downs
- Strain Relief Bend

1 cm (.39 in.) min.

3 cm (1.18 in.) min.
Dr. Collins never places tabs under the skin; he places tabs at least under platysma.

**PULSE GENERATOR**

- 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.
• 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.
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) - this test will verify that Pulse Generator is functioning properly, independent of lead.

- secure Pulse Generator by placing suture through suture hole and attaching it to fascia (not to muscle).

**ASPIRE SR (MODEL 106)**
- Heart Rate–Triggered Vagus Stimulator
  - based on **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.
  - tested intraoperatively to make sure it senses heart rate.

**INTRAOPERATIVE PROGRAMMING**
- set output current 0.25-0.5 mA; leave factory defaults: signal frequency 20 Hz, pulse width 250 microseconds, on time 30 seconds, and off time 5 minutes.

**POSTOPERATIVELY**
- do not program Pulse Generator to ON or periodic stimulation treatment for at least 14 days after initial or replacement implantation.
- neck brace can be used for first week to help ensure proper lead stabilization.
**MRI**

- VNS is only compatible with MRI of head or lower extremities (not for neck / chest / abdomen).
- VNS needs to be turned off by programmer (not by magnet).

**ELECTROSURGERY**

OK to use Bovie if far from VNS.

**PROGRAMMING**

- **current** is increased gradually (up to 2.5 mA); if VNS is implanted for emergency cases (patient in status), current may be ramped up quickly.
- on – 30 seconds; off – 3 minutes
- pulse width 250 msec.
- battery lasts for 10,000 hours of stimulation.

**Right after VNS implantation** (e.g. in OR) – only increase **current** from factory 0 mA to 0.25-0.5 mA; for the rest – leave factory defaults.

**Magnet Mode** – patient can use magnet (e.g. in bracelet) to give additional boost stimulation PRN (e.g. 0.25 mA higher than regular mode with 500 msec pulse width for 60 seconds).
- if seizures are successfully aborted with magnet, increase regular mode current to the one that magnet uses.
- if magnet is held over device for > 65 seconds, device is tuned off and stays off as long as magnet is held on

Cannot test impedances preop if battery is dead.
Normal impedances are < 2000.

**COMPLICATIONS**

1) hoarseness or change in voice (30-50%)
2) infection (3-4%)
3) cough, paresthesia, pain, dyspnea, or headache

**OUTCOMES**

- 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
- 25% of patients with long-term f/u have no benefit!
- up to 8% patients become seizure free.
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."

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


<table>
<thead>
<tr>
<th>Duration</th>
<th>responder rate – VNS registry% (review%)</th>
<th>seizure freedom (Engel Ia) – VNS registry% (review%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 mo</td>
<td>49% (40%)</td>
<td>5.1% (2.6%)</td>
</tr>
<tr>
<td>24-48 mo</td>
<td>63% (60.1%)</td>
<td>8.2% (8%)</td>
</tr>
</tbody>
</table>

- 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).

Seizure freedom, response to treatment, and median seizure reduction from the VNS therapy registry. Across all patients together (A), a progressive increase in seizure freedom was observed after device implantation, paralleling increases in the rate of response to therapy (defined as patients with ≥50% seizure frequency reduction) and the median reduction of seizure frequency. When comparing patients with partial seizures (B) vs generalized seizures (C) as the predominant seizure type, seizure freedom was significantly more likely in patients with generalized seizures at 0 to 4 months (P < .01, Pearson χ2) 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. N = 12,319 visits among 5554 patients, including 4666, 3277, and 3182, and 1194 patients at each follow-up period, respectively.
Seizure freedom rates by age of epilepsy onset and implantation. A, patients who achieve seizure freedom had significantly later onset of epilepsy than those with persistent seizures at 0 to 4 (P < .001, Wilcoxon sum rank test) 4 to 12 (P < .001), 12 to 24 (P < .001), and 24 to 48 (P < .05) months. B, 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). C, 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). N = 12,319 visits among 5,554 patients, including 4,666, 3,277, and 3,182, and 1,194 patients at each follow-up period, respectively.
Seizure freedom and response rate with VNS from systematic literature review. Data compiled from 2869 patients across 78 studies in the systematic review show progressive increase in both seizure freedom and response rate over time, resembling findings from the registry (Figure 1). At latest follow-up, 60% of patients responded to VNS (≥50% reduction in seizures), and 8% were seizure free. N = 650, 405, 1503, 876, and 326 patients at each follow-up period, respectively. VNS, vagus nerve stimulation.
VNS Outcome E01-E05 (Morris et al, Neurology 1999):

<table>
<thead>
<tr>
<th>Duration</th>
<th>% reduction in seizures</th>
<th>% responder rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>1 year</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td>2 years</td>
<td>44%</td>
<td>43%</td>
</tr>
<tr>
<td>3 years</td>
<td>44%</td>
<td>43%</td>
</tr>
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<table>
<thead>
<tr>
<th># AEDS</th>
<th>1 year</th>
<th>2 years</th>
</tr>
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<tbody>
<tr>
<td>-2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>-1</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>No change</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>+1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>+2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
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Czech VNS Study (Kuba et al, Seizure 2009) – all types of seizures:

<table>
<thead>
<tr>
<th>Years f/u</th>
<th>Sz free</th>
<th>&gt; 90% reduc</th>
<th>&gt; 50% reduc</th>
<th>Total RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>3.3%</td>
<td>41.1%</td>
<td>44.4%</td>
</tr>
<tr>
<td>2</td>
<td>3.3%</td>
<td>2.2%</td>
<td>53.2%</td>
<td>58.9%</td>
</tr>
<tr>
<td>5</td>
<td>5.5%</td>
<td>10%</td>
<td>48.9%</td>
<td>64.4%</td>
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DIFFERENT EPILEPSY TYPES

GENERALIZED EPILEPSY

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


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

COST-UTILITY ANALYSIS

EXPLANTATION
- 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, turn stim off for > 3 months to make sure VNS is indeed not helping.