DISCLOSURES

Personal Financial Relationships

None

Off-Label/Investigational Uses

- Stimulation hardware

Other Potential Conflicts of Interest

- Named inventor for intellectual property licensed to Cadence Neuroscience Inc (co-owned by Mayo Clinic)
- Waived contractual rights to royalties
- Principle investigator for the Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study (EPAS)
- Investigator for Mayo Clinic-Medtronic NIH Public Private Partnership (U10-NS065493). Mayo Clinic has received consulting fees on behalf of BNL from Medtronic, Inc, and Philips, Inc.

OBJECTIVES

Upon completion of this CME activity, participants should be able to:

1. Identify characteristics of VNS and DBS
2. Summarize differences between VNS and DBS
**Epilepsy Treatment**

- Medication
- Resection
- Stimulation

**Medication**

- Resection
- Stimulation

**Invasive Brain Stimulation**

**for Epilepsy**

**FDA-Approved**

- Vagus Nerve Stimulation (VNS)
- Responsive NeuroStimulation (RNS)
- Deep Brain Stimulation of Anterior Nucleus of Thalamus (DBS-ANT)

**Off-label or Investigational**

- DBS non-ANT
- Chronic Subthreshold Cortical Stimulation (CSCS)
- Medtronic Investigational RC+S Device

Lundstrom et al, JAMA Neurology, 2016
Kerezoudis et al, J Neurosurg, 2017
Kremen et al, IEEE J Trans Eng Health Med, 2018
Lundstrom et al, Brain Comms, 2019
Starnes et al, Brain Sci, 2019

**Invasive Brain Stimulation**

**STIMULATION PARAMETERS**

- Amplitude
- Frequency
- Pulse width
- Electrode configuration

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Stimulation Strength

- Invasive Brain stimulation
  - Electric field: ~1000 V/m
- TMS
  - Electric field: ~100 V/m
- tDCS
  - Electric field: ~1 V/m
- IOM MEPs
  - Electric field: ~500 V/m


INVASIVE BRAIN STIMULATION
LOCATION AND METHODS OF STIMULATION

Vasilevko, Neurology, 2002

Image courtesy Pixaby

Image courtesy GSV on Flickr

Public domain courtesy Wikipedia Commons

Image courtesy National Library of Medicine

Image courtesy National Library of Medicine
**STIMULATION FOR EPILEPSY TREATMENT**

1880s: J L Corning's "electrocompressor"

1970s-1980s:
- Cerebellar cortex, e.g. Irving S. Cooper
- Thalamus and internal capsule

1990s-2000s:
- Hippocampus and neocortex stimulation

1997: FDA-approval for VNS

2010: SANTE Trial

2011: Responsive cortical stimulation (RNS) trial

2013: FDA-approval for RNS

2018: FDA-approval for DBS ANT

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**VAGUS NERVE STIMULATION**

3-MONTH RANDOMIZED CONTROLLED TRIAL

<table>
<thead>
<tr>
<th>Low Frequency</th>
<th>High Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(n = 102)</em></td>
<td><em>(n = 94)</em></td>
</tr>
<tr>
<td>- 15% Seizure Reduction</td>
<td>- 28% Seizure Reduction</td>
</tr>
<tr>
<td>- 30s / 3 hrs On/Off, 1 Hz</td>
<td>- 30s / 5 min On/Off, 30 Hz</td>
</tr>
<tr>
<td>- 1.2 mA average</td>
<td>- 1.3 mA average</td>
</tr>
</tbody>
</table>

Adverse events: Low vs High
- Voice alteration: 30% vs 66%
- Cough: 43% vs 45%

Vagus nerve stimulation therapy for partial-onset seizures – a randomized active-control trial

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VAGUS NERVE STIMULATION

**VAGUS NERVE STIMULATION EFFICACY**

**Prospective (n = 440)**

- E01-E10 studies
- 44% Seizure Reduction
- 43% Responder Rate

Effective for pediatric patients and Lennox-Gastaut Syndrome

New VNS models sense heart rate


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**VAGUS NERVE STIMULATION HEART RATE SENSING**

**New insertion (n = 51)**

- 59% with at least 50% reduction (17-mo follow-up)

** Stimulator change (n = 62)**

- 53% with at least 50% reduction with old VNS
- 71% of patients reported further 50% reduction with new VNS (13-mo follow-up)


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**VNS Programming**

1. 20 Hz, PW 250 µsec, 30s On / 5 min off
2. Autostim: 20% HR threshold (target ~50 stims/day)
3. 0.125 mA, increase by 0.125 mA per 1-2 weeks
4. Target 1.5-2 mA, then decrease duty cycle
5. For side effects:
   - Decrease amplitude as needed
   - Decrease PW to 125 µsec or Freq to 10 Hz
   - Gradually increase amplitude to 1.5-2 mA
   - Increase PW or freq back to typical settings
ANTERIOR THALAMUS STIMULATION

APPRAOCH
- Transventricular (TV)
  - Standard approach
- Anterior extraventricular (EV)
  - Less accurate than TV
  - TV (n = 31) vs EV (n = 36)
  - 95% vs 71% at target
  - Lehtimaki et al, 2019
- Posterior extraventricular (PEV)
  - 10 patients
  - Feasible, safe, accurate
  - Wang et al, Epi Res, 2019

Lehtimaki et al, Neurosurg, 2019
Wang et al, Epi Res, 2019

EFFICACY AND SIDE EFFECTS
- Approved for focal seizures
- 5-year follow-up
- 68% Median seizure reduction
- 68% Responder rate
- Seizure reduction by location
  - Temporal 76%
  - Frontal 59%
  - Others 68%

Subjective Side Effects
- 15% Depression
- 15% Paresthesia
- 15% Memory impairment
- 9% Anxiety
- 9% Subjective Side Effects

Salvarese et al, Neurology, 2015

ANTERIOR THALAMUS STIMULATION
Cognitive and Mood Side Effects

- Improved subjective cognitive function years 1-5 (Salanova et al, Neurology, 2015)
- No decline in cognitive or depression scores at 7 years (Troster et al, Seizure, 2017)
- 4/22 patients with mood, anxiety or psychosis relieved by programming changes (Jarvenpaa et al, Epilepsia, 2018)

Subjective Side Effects
- Depression: 15%
- Anxiety: 9%
- Paresthesia: 9%
- Subjective Memory impairment: 13%

ANTERIOR THALAMUS STIMULATION
2020 Device with Sensing

- FDA-approved for focal epilepsy
- 2 leads, 8 channels
- Primary cell, similar battery life
- MRI 3T conditional
- Limited sensing, 2 channels
  - Frequency domain, averaged q10 min
  - Power-in-band, 2, 5 Hz width
  - Monopolar stimulation bracketed by sensing
- Unlosable features: 16 channels, 6 sensing

DBS-ANT Programming

2-4 weeks following implant:
1. 145 Hz, PW 95 µsec, 1 min on / 5 min off
2. Single monopolar cathode(-) per side per imaging
3. Start 3 mA per cathode

2-4 months following implant:
1. Increase to 5 mA

2-4 months following implant:
1. Double monopolar / add second cathode, decrease current 30-50%
2. Change cathode location
3. Decrease duty cycle
4. Decrease stimulation frequency

Side effects:
1. Decrease amplitude by 30-50%
2. Decrease stimulation frequency
3. Bipolar stimulation
4. 1-3 cathodes, 1 anode per lead
Centromedian DBS
Generalized Epilepsy

- 20 adults with generalized epilepsy
- 8-66 seizures per day
- Continuous bipolar stimulation
  - 130 Hz, 300 µsec, 3.4-5 V (mean)
- Median follow-up: 2.5 years
- Seizure reduction: 79%
- Responder rate: 90%


DBS CM +/- ANT
Generalized/Mixed Epilepsy

- Retrospective study
- 16 children and adults
- Generalized, multifocal, poorly localized, and posterior onset seizures
- 0.3-100 seizures per day
- Continuous centromedian (CM) stimulation
  - 11/16 patients with Anterior Nucleus (ANT)
  - 5-100 Hz, 90-210 µsec, 2.2-6.9 V
  - 14/16 EMU stimulation optimization
- Median follow-up: 6.7 yrs
- Seizure reduction: 58%
- Responder rate: 63%


Chronic Subthreshold Stimulation

- 26 yo RH man, R perinatal infarct
- Refractory focal seizures with impaired awareness episodes
- EEG w/o clear seizure localization
- Trial stimulation for several days
- Off-label chronic subthreshold cortical stimulation (CSCS)
- Eventual seizure freedom
- Case series with 21 patients
  - Slower <4 Hz EEG as excitability biomarker

Lundstrom et al, Epi Behav Rep, 2020
Lundstrom et al, Clin Neurophysiol 2018;
Lundstrom et al, Brain Comm, 2019;
Lundstrom et al, Sci Rep 2019
WHAT I TELL PATIENTS

- RNS and DBS-AANT: 50% seizure reduction after 1 year
- VNS: somewhat less efficacy but also not brain surgery
- Results tend to improve over time
- RNS involves a skull-mounted device; DBS-AANT and VNS are chest implants
- RNS has diagnostic benefits; DBS-AANT allows for patient adjustments
- These devices are MRI-conditional
- Often there is more than one good option

Thank you!

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- NIH NINDS K23

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  - Neurology Department, Mayo Clinic
  - Neurosurgery Department, Mayo Clinic