Neuro-modulatory Devices in Epilepsy Treatment
Approved Alternative Surgical Therapies

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Cleveland Clinic Epilepsy Update & Review

DISCLOSURES:
Grant/Research Support:
• NIH RO1 (RO1NS089212) A Brain Atlas for Mapping Connectivity in Focal Epilepsy
• NIH RO1 (RNS097719A) Nomogram to Predict Seizure Outcome
• NeuroPace Long term Treatment Trial & Post Approval Study
• Medtronic Post Approval Study
• Brain Sentinel
Speaker’s Bureau:
• NeuroPace
Consultant:
• NeuroPace
Major Shareholder:
• None
Objectives

Review neuromodulatory therapy in epilepsy and their efficacy, adverse effects and safety data for:
- Vagus nerve stimulation
- Brain responsive neurostimulation
- Deep brain stimulation of the anterior nucleus of thalamus
Neuromodulation

Targets for Stimulation
- Cerebellum
- Hippocampus
- Subthalamic Nucleus
- Caudate Nucleus
- CentroMedian Nucleus
- Anterior Nucleus of the Thalamus
- Various individualized cortical sites
- Vagus Nerve
- Trigeminal Nerve

Types of Stimulation
- Open Loop
- Closed Loop

Safety of Stimulation
- Electrical stimulation of brain tissue
  - Less than 30µC/cm²/phase

Nune G et al. Curr Treat Opions Neurol 2012
Neuro-Modulation

Versus Medicine/Surgery

• Lack typical systemic or neurological sided effects
• Stimulation related side effects
  - Intracranial stimulation
  - VNS stimulation
• Surgically implanted
  - Surgical complications
  - Battery replacement
  - Less invasive
  - Reversible

Versus Medicine/Surgery

• Improvement of efficacy over time

Nune G et al. Curr Treat Opions Neurol 2012
Parameters of Stimulation

- Anode/Cathode contacts
- Stimulation Frequency
- Stimulation Duration
- Stimulation Intensity
- Stimulation Field
- Pulse Duration
Vagus Nerve Stimulation (VNS)
VNS

- FDA approval in 1997
- Indicated for adjunctive therapy for drug resistant partial epilepsy
  - Commonly used in generalized epilepsy
  - Approved for depression
    - But not reimbursed
- In adults and adolescents over 4 years (approved June 2017)
- More than 100,000 patients implanted

Wheless JW et al. Epilepsy Behav 2018
Mechanism

• Unknown
• Vagus nerve parasympathetic nerve also part of the interoceptive pathway
• Stimulation ascending via brainstem nuclei and diffusely modulating cortical excitability
  - Patients with good efficacy showed decrease metabolic activity on functional imaging studies bilaterally during ON stimulation

Vagus Nerve Stimulation

- **Open Loop**
  - Optional cardiac detection (closed loop adjunct)
    - Provides stimulation to tachycardia (at least 20%)  
    - AspireSR model  
    - June 2015
  - Patient activated by magnet

- **Subcutaneous implantation**
  - Generator in left subclavicular fossa
  - Electrode left vagus

Fridley J et al. Neurosurg Focus 2012

Nune G et al. Curr Treat Opions Neurol 2012
### TABLE 1: Summary of Class I, II, and III evidence of VNS efficacy in treating epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Seizure Type</th>
<th>Notes</th>
<th>Follow-Up</th>
<th>No. of Centers</th>
<th>Median or Mean % Seizure Reduction</th>
<th>% Patients w/ &gt;50% Reduction†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I evidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Blinded randomized control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ben-Menachem et al., 1994</td>
<td>114</td>
<td>partial</td>
<td>high vs low stim comparison</td>
<td>3 mos</td>
<td>multi</td>
<td>25 vs 6</td>
<td>31</td>
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<tr>
<td>Handforth et al., 1998</td>
<td>196</td>
<td>partial</td>
<td>high vs low stim comparison</td>
<td>3 mos</td>
<td>multi</td>
<td>28 vs 15</td>
<td>23</td>
</tr>
<tr>
<td>Amar et al., 1998</td>
<td>17</td>
<td>partial</td>
<td>high vs low stim comparison</td>
<td>3 mos</td>
<td>single</td>
<td>71 vs 6</td>
<td>57</td>
</tr>
<tr>
<td><strong>Class II evidence</strong></td>
<td></td>
<td></td>
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<tr>
<td>Non-blinded randomized control</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scherrman et al., 2001</td>
<td>28</td>
<td>mixed</td>
<td>2 stim paradigms</td>
<td>NR</td>
<td>single</td>
<td>30 overall</td>
<td>45</td>
</tr>
<tr>
<td>DeGiorgio et al., 2005</td>
<td>61</td>
<td>partial</td>
<td>3 stim paradigms</td>
<td>3 mos</td>
<td>multi</td>
<td>26 overall</td>
<td>29</td>
</tr>
<tr>
<td><strong>Class III evidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prospective observational clinical studies</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ben-Manachem et al., 1999</td>
<td>64</td>
<td>mixed</td>
<td></td>
<td>3–6 mos</td>
<td>single</td>
<td>NR</td>
<td>45</td>
</tr>
<tr>
<td>Parker et al., 1999</td>
<td>15</td>
<td>mixed</td>
<td>children w/ encephalopathy</td>
<td>1 yr</td>
<td>single</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Labor et al., 1999</td>
<td>24</td>
<td>gen</td>
<td></td>
<td>3 mos</td>
<td>single</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>DeGiorgio et al., 2000</td>
<td>195</td>
<td>mixed</td>
<td></td>
<td>12 mos</td>
<td>multi</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Chavel et al., 2003</td>
<td>29</td>
<td>partial</td>
<td></td>
<td>1–2 yrs</td>
<td>single</td>
<td>53</td>
<td>54‡</td>
</tr>
<tr>
<td>Vonck &amp; colleagues, 1999 &amp; 2004</td>
<td>118</td>
<td>mixed</td>
<td></td>
<td>&gt;6 mos</td>
<td>multi</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Majoe &amp; colleagues, 2001 &amp; 2005</td>
<td>19</td>
<td>mixed</td>
<td>children w/ encephalopathy</td>
<td>2 yrs</td>
<td>single</td>
<td>20.6</td>
<td>21</td>
</tr>
<tr>
<td>Huf et al., 2005</td>
<td>40</td>
<td>NR</td>
<td>adults w/ low IQ</td>
<td>2 yrs</td>
<td>single</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Kang et al., 2006</td>
<td>16</td>
<td>mixed</td>
<td>children</td>
<td>&gt;1 yr</td>
<td>multi</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ardeche et al., 2007</td>
<td>19</td>
<td>partial</td>
<td></td>
<td>&gt;2 yrs</td>
<td>single</td>
<td>25§</td>
<td>33§</td>
</tr>
</tbody>
</table>

* gen = generalized; multi = multiple; NR = not reported; stim = stimulation.
† Refers to “high” stimulation group only.
‡ At 1 year.
§ At 2 years.

### TABLE 1. Stimulation parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical</th>
<th>Range</th>
<th>Typical</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output current (mA)</td>
<td>1.5</td>
<td>0.25–3.0</td>
<td>1.25</td>
<td>0.25–3.0</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>30</td>
<td>20–50</td>
<td>1</td>
<td>1–2</td>
</tr>
<tr>
<td>Pulse Width (μs)</td>
<td>500</td>
<td>500–1300</td>
<td>300</td>
<td>300–1300</td>
</tr>
<tr>
<td>On time (s)</td>
<td>30</td>
<td>30–90</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Off time (min)</td>
<td>5</td>
<td>5–10</td>
<td>90</td>
<td>60–180</td>
</tr>
<tr>
<td>Magnet parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Output current (mA)</td>
<td>1.5</td>
<td>0.5–3.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>On time (s)</td>
<td>30</td>
<td>30–90</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pulse width (μs)</td>
<td>500</td>
<td>500</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, Magnet output was set to 0 in the low group: no current delivered.
Seizure Free, Responder Rate, Engle Classification

Englot DJ et al. J Neurosurg 2016
Efficacy

TABLE 2: Seizure outcomes reported by Engel class

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I, 100%</th>
<th>II, &gt;90%</th>
<th>III, 50%--90%</th>
<th>IV, &lt;50%</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (%)</td>
<td>121 (4.6)</td>
<td>200 (7.6)</td>
<td>1012 (38.4)</td>
<td>1301 (49.4)</td>
<td>2634</td>
</tr>
</tbody>
</table>

* Only individuals for whom Engel classification could be determined are tallied.
Adverse Effects

Serious adverse effects: Vocal cord paralysis 1%; infection 1.5%

Englot DJ et al. J Neurosurg 2011
VNS Stimulation Parameters

- Begin 0.25mA
  - Gradually increase 0.25mA steps
  - Up to 1-1.5mA or more
- Frequency 20-30Hz
- Pulse width 250-500 µs
- 30 seconds on
- 5 minutes off

- Side effect may improve
  - Reduction of pulse width to 250µs
  - Reduction of frequency to 20hz
- Improve efficacy
  - Increase duty cycle by reducing off time
    - Do not exceed 50% duty cycle

Nune G et al. Curr Treat Opions Neurol 2012
Responsive Neural Stimulation (RNS)
Responsive Neural Stimulation

- Medically refractory focal epilepsy
  - Failure of more than 2 ASD
- 18 years or older
- FDA approved 2013
- Implantation
  - Device within the skull
  - Combination of 1-2 depths or subdural strips over seizure focus
- No more than two (2) ictal onsets

- Closed loop
- Stimulation usually does not cause appreciable symptoms
- Stores ECoG
- Seizure detections algorithms programmed

Nune G et al. Curr Treat Opions Neurol 2012
The RNS® System

Neurostimulator and Leads

Programmer

Patient Data Management System (PDMS)

Remote Monitor

NeuroPace®
RNS Stimulation Parameters

- Five sequential stimulations
  - Rapid succession
  - Each two bursts
- Starting 1mA
  - Adjust up to 3µC/cm²/phase
- Pulse width 160µs
- Frequency 200 Hz
- Burst duration 100ms

- Polarity of electrodes can be configured
  - Close bipolar within electrode (+-+- and +++)
  - Wide bipolar across electrode (+++ and ----)
  - From electrode to generator cover

Nune G et al. Curr Treat Opions Neurol 2012
Primary Effectiveness Endpoint

% Change in Seizure Frequency (GEE)

Entire Blinded Evaluation Period

Post-op Month of Blinded Evaluation Period

Treatment

Sham

Morrell M et al. Neurology 2011
75% Median Seizure Reduction at Year 7

In year 7, 35% of patients had seizure reduction of ≥90%

Similar response regardless of
- Number of seizure foci
- Seizure onset location
- MRI abnormality
- Prior epilepsy surgery
- Prior VNS
- Prior intracranial monitoring

Nair D. et a. Neurology 2020
Meaningful Seizure Free Periods

28% (72/256) had at least 1 period of ≥ 6 months of seizure freedom

18% (47/256) had at least 1 period of ≥ 12 months of seizure freedom

- These patients had an average of 3.2 years as the longest consecutive period of seizure freedom
Pivotal Study: SAEs Affecting ≥ 2.5% of Subjects, 2 Yrs Post-Implant

<table>
<thead>
<tr>
<th></th>
<th>% Subjects with events (# subjects)</th>
<th>% Subjects with Device-Related¹ Events (# subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Related to the implanted device</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant site infection</td>
<td>3.7% (7)</td>
<td>3.7% (7)</td>
</tr>
<tr>
<td>Device lead revision</td>
<td>3.7% (7)</td>
<td>2.1% (4)</td>
</tr>
<tr>
<td>Device lead damage</td>
<td>2.6% (5)</td>
<td>2.6% (5)</td>
</tr>
<tr>
<td><strong>Related to seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex partial seizures increased</td>
<td>5.2% (10)</td>
<td>3.1% (6)</td>
</tr>
<tr>
<td>Tonic-clonic seizures exacerbated</td>
<td>3.7% (7)</td>
<td>0.5% (1)</td>
</tr>
<tr>
<td>Tonic-clonic seizures increased</td>
<td>3.7% (7)</td>
<td>2.6% (5)</td>
</tr>
<tr>
<td><strong>Other serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG monitoring</td>
<td>7.3% (14)</td>
<td>0.5% (1)</td>
</tr>
<tr>
<td>Death</td>
<td>3.1% (6)</td>
<td>0.5% (1)</td>
</tr>
<tr>
<td>Therapeutic agent toxicity²</td>
<td>2.6% (5)</td>
<td>--</td>
</tr>
</tbody>
</table>

¹ Includes device-related and device-relation uncertain
² Four related to antiepileptic medication and 1 to acetaminophen toxicity

- The risk for infection is 4.1% with each RNS neurostimulator procedure
  - Over 1895 patient-implant years, serious device-related implant site infection was reported in 12.1%
  - All but one of the infection involved only soft tissue and cultures most often indicated skin flora
- No instances of meningitis or brain parenchymal infection
- Non-seizure related hemorrhage occurred in 7 patients (2.7%)

Morrell M et al. Neurology 2011

Nair D. et al. Neurology 2020
Cognition, Mood and Quality of Life
Pivotal Study

• No adverse effects on cognition\(^1\)
  - No difference between Treatment and Sham at end of Blinded Evaluation Period
  - No deterioration in any group scores, including memory

• No adverse effects on mood\(^2\)
  - No difference between Treatment and Sham at end of Blinded Evaluation Period
  - No deterioration at any time point in group scores

• Clinically significant improvements in Quality of Life\(^3\)
  - Blinded Period: 36.6% Treatment; 39.1% Sham
  - Open Label: 38% 1 year; 44% 2 years

Morrell M et al. Neurology 2011
Safety SUDEP Rate

• Rate of probable or definite SUDEP combined was **2.8 per 1000** patient stimulation years (95% CI: 1.2-6.7) and 3.2 per 1000 patient implant years (95% CI: 1.4-7.0).

Nair D et al. Neurology 2020
Deep Brain Stimulation (DBS)
Deep Brain Stimulation

- DBS provides open loop stimulation
- Bilateral anterior nucleus of the thalamus stimulation
- DBS of other targets remains inconclusive

- Approved in Europe (September 2010), Canada (March 2012), Australia (2015)
- Approved in USA (April 2018)
  - Patients 18 years and older
  - Focal / Partial Epilepsy
  - Medically intractable (failed more than 3 AEDs)
**DBS RCT and Long Term Efficacy**

*Romanized to receive either 5V or 0V for 3 months double blind then conversion to 5V for all subjects*

<table>
<thead>
<tr>
<th>Randomized Control Trial*</th>
<th>Total # of Seizures: decreased by 40% at 3 months in DBS group and by 15% in patient not receiving DBS</th>
<th>Fisher RS, et al. Epilepsia. 2010 May; 51(5):899-908</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seven Year Follow up of Patients in RTC</td>
<td>Median percentage seizure reduction of 75%</td>
<td>Sandok E, et al. American Epilepsy Society Annual Meeting. 2016 Abst. 1.298.</td>
</tr>
</tbody>
</table>
Seizure Reduction Over Time

Variation of Response 5 Years

- Median percentage reduction of seizure – 69%.
- Responder rate – 68%.
- Greater than 50% increase in seizures – 3%.
- Seizure free – 19%.

DBS Serious Adverse Effects

35.5% Device Related SAE (39 out of 110 patients)

**Surgical SAE**
- Implant Site Infection – 10%
- Leads not at target – 8.2%

**Cognitive SAE & Status Epilepticus**
- Depression 37.3%
  - 41 pts – of which 66% had H/O depression
  - 11.8% suicidal ideation (13 pts)
    - One completed suicide
- Memory Impairment 27.3%
  - 50% had H/O memory impairment
- Status Epilepticus 6.4%
  - 3 out of 7 pts not receiving stimulation

**Sudden Unexplained Death**
- 7 Deaths – none device related
  - 2 Definite SUDEP
  - 1 Probable SUDEP
  - 1 Possible SUDEP

Memory and Mood in Anterior Thalamic DBS for Epilepsy

• No significant cognitive declines or worsening memory
  - Blinded phase or at 7 years
• Higher scores of executive function and attention were measured at 7 years
• Memory and depression AEs were not associated with:
  - Objective measures
  - 7 year neurobehavioral outcome
  - Worsening quality of life measures
  - Demographic
  - Seizure characteristics
  - Change in seizure frequency
  - Frequency of AEs

Conclusion

- Neuromodulatory therapy in epilepsy allows for adjunctive therapy for patients who are medically intractable and are not good candidates for epilepsy surgery
- Neuromodulation appears to have improved efficacy over time
- Safety data and adverse effects are different than those related to medications or surgery