Devices for Non-Lesional Epilepsy

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## Disclosures

<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrainVital</td>
<td>Founder, SAB</td>
</tr>
<tr>
<td>Neuropace</td>
<td>Consultant, Investigator</td>
</tr>
<tr>
<td>Sage Therapeutics</td>
<td>Consultant</td>
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<tr>
<td>Upsher-Smith Laboratories</td>
<td>Consultant</td>
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<tr>
<td>Eisai</td>
<td>Consultant</td>
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American Epilepsy Society | 2013 Annual Meeting
Learning Objectives

• Become familiar with data on devices for non-lesional epilepsy
• Consider issues related to device-based treatment for non-lesional epilepsy
Brain Stimulation for Epilepsy

• Substrate modification/Prophylaxis
  – Event-independent
  – Anatomically broad?
  – Modulatory

• Seizure termination/Abortive Rx
  – Event-dependent
  – Anatomically precise?
  – Detection required
Devices for Epilepsy Treatment

- Vagal Nerve Stimulator
- Responsive Neural Stimulator
- Deep Brain Stimulator

- Trigeminal Nerve Stimulator
- Transcranial Magnetic Stimulation
- Transcranial DC Stimulation
- Amygdalo-hippocampal Stimulation
Vagal Nerve Stimulation: Clinical Trials

- E 03
- E 05

- Medically intractable Sz
- > 5 Sz/month
- “Predominantly partial”
- No characterization with regard to lesion status
- Randomized to high- vs. low-intensity stimulation
VNS E 03 Results

**Individual Patients**

**Seizure Frequency Relative to Baseline**

**HIGH**

**LOW**

<table>
<thead>
<tr>
<th>N</th>
<th>'High'</th>
<th>'Low'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Mean % Change</td>
<td>-4.5%</td>
<td>-6.1%</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>-14.1% to -34.9%</td>
<td>3.6% to -15.8%</td>
</tr>
<tr>
<td>p value (within group)</td>
<td>&lt;0.01</td>
<td>&gt;0.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>'High'</th>
<th>'Low'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Seizures/Day-Baseline</td>
<td>0.73</td>
<td>0.82</td>
</tr>
<tr>
<td>Seizures/Day-Stimulation</td>
<td>0.42</td>
<td>0.80</td>
</tr>
<tr>
<td>p value (within group)</td>
<td>&lt;0.01</td>
<td>&gt;0.19</td>
</tr>
<tr>
<td>p value (between groups)</td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>
SANTE Deep Brain Stimulator Clinical Trial

- Age 18-65
- >5 partial Sz/month X 3 months
- Failed >2 AEDs
- On 1-4 AEDs at stable dosing
- No progressive lesion (status otherwise uncategorized)
- Bilateral stereotaxic implantation with target confirmation after 3 month baseline period
- Randomized and treated 1 month after implant
- 3 month blinded trial period
Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy

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**Timeline**

- **Screen**
  - Mo (-3) - 0
- **Baseline**
  - Mo 0
- **Implant**
  - Mo 1-4
  - ½ On & ½ Off
- **Blinded**
  - Mo 1-4
  - All On
- **Open-label**
  - Mo 4-13
  - All On
- **Long-term follow-up**
  - Any safe parameter

**Study Process**

- Signed Consent = 157
  - Discontinued = 9
- Completed Baseline = 148
  - Discontinued = 38
- Implanted = 110
  - Skip Blinded = 2
- Completed Blinded Phase = 108
  - Discontinued = 5
- Enter Long-Term = 105
  - Discontinued = 3
  - 2 years (25 months) = 102
  - Discontinued > 2 years = 11

91 subjects remain active in the study

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Epilepsia


SANTE Stimulation Parameters

• 5 V or 0 V (control)
• 90us pulses
• 145 pulses/s
• ON 1 min
• OFF 5 min
Treatment with DBS Reduced Sz frequency during the blinded period

Table 2. GEE Model adjusted mean percent difference in seizure frequency

<table>
<thead>
<tr>
<th></th>
<th>Month 1–2</th>
<th></th>
<th>Month 2–3</th>
<th></th>
<th>Month 3–4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted %</td>
<td>p-value</td>
<td>Adjusted %</td>
<td>p-value</td>
<td>Adjusted %</td>
<td>p-value</td>
</tr>
<tr>
<td>Adjusted % difference^a</td>
<td></td>
<td></td>
<td>Adjusted %</td>
<td>p-value</td>
<td>Adjusted %</td>
<td>p-value</td>
</tr>
<tr>
<td>Adjusted % difference^a</td>
<td></td>
<td></td>
<td>Adjusted %</td>
<td>p-value</td>
<td>Adjusted %</td>
<td>p-value</td>
</tr>
<tr>
<td>All participants—primary analysis (active n = 54, control n = 54)</td>
<td>20%</td>
<td>0.50</td>
<td>-10%</td>
<td>0.40</td>
<td>-29%</td>
<td>0.0017</td>
</tr>
<tr>
<td>With outlier excluded (active n = 53, control n = 54)</td>
<td>-10%</td>
<td>0.37</td>
<td>-11%</td>
<td>0.34</td>
<td>-29%</td>
<td>0.0023</td>
</tr>
<tr>
<td>ITT (active n = 54, control n = 55)</td>
<td>19%</td>
<td>0.52</td>
<td>-10%</td>
<td>0.40</td>
<td>-29%</td>
<td>0.0016</td>
</tr>
<tr>
<td>ITT with outlier excluded (active n = 53, control n = 55)</td>
<td>-11%</td>
<td>0.34</td>
<td>-11%</td>
<td>0.34</td>
<td>-29%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Overall estimate</td>
<td>-17%</td>
<td>0.039</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SANTE Median Seizure Frequency

The graph shows the median seizure frequency percent change from baseline for different phases of the study. The x-axis represents 1-month groupings: Baseline, Operative (1 month), Month 1-2 (1 month), Month 2-3 (1 month), and Month 3-4 (1 month). The y-axis represents the percent change in median seizure frequency.

- The green line with filled circles represents the active (stimulated) group, showing a decreasing trend with percent changes of -22.2%, -25.3%, -28.7%, and -40.4% at each phase.
- The red line with open squares represents the control group, showing a decreasing trend with percent changes of -21.3%, -33.9%, -42.1%, and -14.5% at each phase.

The graph indicates a significant reduction in seizure frequency over the study period for both groups, with the active group experiencing a more pronounced decrease compared to the control group.
SANTE Seizure Frequency Reduction
(>25 month follow-up, n=81)
Closed Loop Stimulation

- Stimulation delivered in response to an event-determined trigger
- Loop may be closed by patient, observer, seizure detection device, or seizure-associated event detection system, e.g. HR change, accelerometer measurements etc.
- May include feedback component with evaluative strategy to determine if stimulation has been successful
- Primary intent is to abort events, not to modify substrate
Spontaneous Epileptiform Activity Terminated with Cortical Stimulation
Neuropace RNS Clinical Trials

- Feasibility Trial
- Pivotal Trial

- One or two discrete foci
- Unable or unwilling to have resective surgery
  - Unacceptable risk of memory impairment
  - Lesion/focus in eloquent area
- Residual incompletely resectable lesion
Patient Selection

- One or two discrete foci
- Unable or unwilling to have resective surgery
  - Unacceptable risk of memory impairment
  - Lesion/focus in eloquent area
- Residual incompletely resectable lesion
Detection Algorithm

- Initial exploration via line length algorithm
- Subsequent refinement via frequency analysis. Limited to 125 Hz.
- Generally stable after customization for individual subjects
Treatment Parameters

• Highly customized
• Typical parameters
  – 1.5 to 3 µC/cm$^2$ Charge density
  – 5-10 mAmp stimulation intensity
  – 100-150 Hz stimulation frequency
  – 100-300 msec train duration
  – 100-400 µsec pulses
• Analysis of optimal parameters underway (Morrell, personal communication)
RNS System Pivotal Trial: Randomized double-blinded sham stimulation controlled

Two investigator teams at each site

- **Assessment Physician (blinded):** Collected effectiveness and safety data
- **Treatment Physician (not blinded):** Managed device but did not collect effectiveness data
Treatment with the RNS System reduced seizures during the blinded period

- The implant procedure caused a temporary reduction in seizures
- Responsive stimulation caused a sustained reduction in seizures

<table>
<thead>
<tr>
<th></th>
<th>Mean % Change in Seizure Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (N=97)</td>
</tr>
<tr>
<td>Entire Blinded Evaluation Period (N=191)</td>
<td>-37.9%</td>
</tr>
<tr>
<td>Month 1</td>
<td>-34.2%</td>
</tr>
<tr>
<td>Month 2</td>
<td>-38.1%</td>
</tr>
<tr>
<td>Month 3</td>
<td>-41.5%</td>
</tr>
</tbody>
</table>

1 Based on agreed upon GEE
Pivotal Trial: Mean Disabling Seizures, Observed Data (N=191)

CAUTION--Investigational device. Limited by United States law to investigational use.
Seizure reduction is sustained over long term follow-up

- N values reflect maximum follow-up times
- Mean patient follow-up is 3.3 years
Anatomical Abnormalities in All Subjects (N= 247)

- None, 38.5%
- Sclerosis, 25.5%
- Dysplasia, 16.6%
- Sclerosing, 6.5%
- Encephalomalacia, 5.7%
- Multiple, 3.2%
- Surgical, 2.0%
- Vascular, 1.2%
- Tumor, 0.8%
There is **no statistically significant difference** in percent seizure reduction between subjects with anatomical abnormalities and non-lesional subjects (62% and 52%, respectively; \( p = 0.1079 \), Wilcoxon Rank Sum Test)

- Most recent 3 months of seizure data in Long Term Treatment Trial
- All Subjects, Last Observation Carried Forward (N=247)

Error bars indicate 25th and 75th percentiles
Anatomical Abnormalities in Subjects with MTL Onsets Only (N=106)

- Sclerosis, 52.8%
- None, 32.1%
- Other/Unknown, 5.7%
- Dysplasia, 3.8%
- Multiple, 2.8%
- Encephalomalacia, 1.9%
- Vascular, 0.9%
Subjects with MTL Onsets Only (N=106)

• Most recent 3 months of seizure data in Long Term Treatment Trial

• Subjects with MTL Onsets Only, Last Observation Carried Forward

Error bars indicate 25th and 75th percentiles
Anatomical Abnormalities in Subjects with Neocortical Onsets Only (N=122)
Subjects with Neocortical Onsets Only (N=122)

- Most recent 3 months of seizure data in Long Term Treatment Trial
- Subjects with Neocortical Onsets Only, Last Observation Carried Forward

Error bars indicate 25\textsuperscript{th} and 75\textsuperscript{th} percentiles
Conceptual Challenges in Closed-Loop Stimulation

- Detector accuracy (sensitivity vs. specificity)
  - Safety of extra stimulation
  - Cost of missed detections
  - Functional effect of stimulation
  - Power consumption
- Prediction vs. Detection vs. Modification
- Sampling site vs. treatment site
Detection Characteristics

Detector Accuracy vs Detection Utility

Prediction

Detection

$t_0$
Detection Problems

• False detections (sensitivity vs. specificity)
  – High sensitivity but low specificity yields inappropriate stimulation
  – In the extreme, may be almost continuous (>1300/day in some RNS patients): 600/d typical (<5 mins total stimulation)
  – Lead to excess power consumption

• Late detections (clinical utility)
  – Later detections are more sensitive
  – Later detections are less useful

• Missed detections (breakthrough Sz)
  – Low sensitivity even with high specificity yields failed treatment
Detection Problems (Cont.)

• Sampling issues
  – Sampling is spatially limited
  – Co-incidence of detection site and treatment site is not assured

• Detection algorithms are imperfect
Treatment Issues

• Patient selection
• Defining the site for treatment
• Achieving adequate spatial coverage of critical area
• Optimizing treatment parameters
• Incorporating feedback control/iterative approach
Ideal Candidates for Focal Closed Loop Stimulation

• Zone of epileptogenesis
  – Exquisitely focal
  – Well documented
  – Spatially restricted

• Adequate warning to support detection prior to impairment of consciousness
Focal Closed Loop Stimulation: Future Directions

• Increase spatial coverage
• Optimize detection system
• Optimize stimulation parameters
  – Anatomic specificity
  – Time into Seizure
  – Incorporate iterative analysis/response
## Subject Characteristics

<table>
<thead>
<tr>
<th>Study (Pub date), n implanted</th>
<th>VNS E 03 (1995), n=104</th>
<th>DBS SANTE (2010) n=110</th>
<th>RNS PIVOTAL (2011) n=191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant (years)</td>
<td>33.3</td>
<td>36.1 ± 11.2</td>
<td>34.9 ± 11.6</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>38%</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
<td>21.6</td>
<td>22.3 ± 13.3</td>
<td>20.5 ± 11.6</td>
</tr>
<tr>
<td>Daily AEDs at enrollment</td>
<td>2.09</td>
<td>2.3 ± 0.68</td>
<td>2.8 ± 1.2</td>
</tr>
<tr>
<td>Seizures/28 days (mean)</td>
<td>44.8</td>
<td>19.5</td>
<td>34.2</td>
</tr>
<tr>
<td>Prior VNS</td>
<td>N/A</td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td>Prior epilepsy surgery</td>
<td>Unknown</td>
<td>24%</td>
<td>32%</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>Unknown</td>
<td>60% temporal</td>
<td>50%</td>
</tr>
<tr>
<td>Multifocal/Diffuse</td>
<td>Unknown</td>
<td>10%</td>
<td>55%</td>
</tr>
<tr>
<td>Author</td>
<td>Study</td>
<td>Modality</td>
<td>Arms</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>VNS Study Group (Salinsky), 1995</td>
<td>E03</td>
<td>VNS</td>
<td>High v. Low</td>
</tr>
<tr>
<td>Handforth et al., 1998</td>
<td>E05</td>
<td>VNS</td>
<td>High v. Low</td>
</tr>
<tr>
<td>Fisher et al., 2010</td>
<td>SANTE</td>
<td>Anterior Nucleus DBS</td>
<td>Active v. Sham</td>
</tr>
<tr>
<td>VNS Study Group (Morrell), 2011</td>
<td>RNS Pivotal</td>
<td>RNS</td>
<td>Active v. Sham</td>
</tr>
</tbody>
</table>
Conclusions

• No significant data specifically focused on stimulation for non-lesional epilepsy
• Subject characteristics in randomized device studies are similar
• Efficacy of intracranial approaches seems higher, but distinction between targeted and modulatory strategies is uncertain
• Differences in efficacy between in RNS and DBS in extra-temporal disease may become critical in patient selection
• Distinction between substrate modification and targeted responsive approaches is not black and white
• Goal of treating the most restricted brain region possible consistent with achieving a good result seems reasonable
• Ultimately targeted approaches are likely to be preferred in well circumscribed disease, whereas modulatory approaches may be preferred in poorly localized disease