Responsive Neurostimulation for the Treatment of Epilepsy: Has the Future Arrived?
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New York, NY
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But some data for this presentation were provided by Neuropace and not yet published in peer-reviewed literature

Name of Commercial Interest

Type of Financial Relationship

NOTE: Responsive Neurostimulation for epilepsy is not approved by the F.D.A.
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Emory: R Gross
GWU: J Leiphart
Henry Ford Hosp: G Barkley
Indiana Univ: V Salanova
JHU: G Bergey
Mayo-AZ: R Zimmerman
Mayo-FL: R Wharen
Mayo-MN: WR Marsh
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U Rochester: M Berg / AJ Fessler
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UVA: N Fountain
U Wisconsin: P Rutecki
Via Christi: A Massey
Wake Forest: W Bell
Yale: R Duckrow
Clinical Observation

Applied cortical stimulation disrupts afterdischarge induced during functional mapping
Responsive Stimulation Aborts Induced Afterdischarges in Humans

- Lesser RP et al., Neurology 1999
  - 17 patients with subdural electrodes
  - Brief bursts of pulse stimulation (used 50 Hz) aborted induced afterdischarges but did not induce clinical seizures
  - Stimulation of shorter durations (0.5-1s) were more effective than longer durations (1.5 – 2s)

- Also noted by Penfield and Jasper in the operating room in the 1950s

- Osorio et al, Annals Neurology 2005
  - 4 local closed-loop stimulation at the seizure focus, 4 remote closed-loop stimulation to the anterior nucleus of the thalamus
  - Overall, 5/8 were responders (>50% improvement)
  - Local closed-loop: 55% decrease in seizures
  - Remote closed-loop: 41% decrease
Aborted aura
Responsive Neurostimulation for Treatment of Epilepsy

- Stimulation delivered at the time and site of detection, before spread or symptoms
- “Automated Implantable Cerebral Desynchronizer”
- Applied to partial onset seizures with or without secondary generalization
- Patients with one or two foci
- ≥3 seizures/month
- Adequately localized
- One or two leads at a time
- Depths or strips
Responsive Neurostimulator System

Implantable Responsive Neurostimulator

Programmer

Patient Data Management System (PDMS)

Leads (depth and strip)
Cosmetics
Placement of ferrule
Placement of RNS device within ferrule
Anterior Lead (A)

Posterior Lead (P)

Parahippocampal Longitudinal Strip (not connected)
Hippocampal depth lead

Parahippocampal strip
RNS Pivotal Trial

Multi-center, prospective, randomized, double-blinded, sham-controlled study of individuals 18 - 70 years of age with medically intractable seizures (>3/month) localized to 1 or 2 foci.
Pivotal Trial: Subject Demographics
N=191 subjects from 32 sites

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (18-66)</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
<td>20 (2-57)</td>
</tr>
<tr>
<td>Prior VNS</td>
<td>34%</td>
</tr>
<tr>
<td>Prior Epilepsy Surgery</td>
<td>32%</td>
</tr>
<tr>
<td>Median Baseline Seizure Rate</td>
<td>10 / 28 days</td>
</tr>
<tr>
<td>Mesial temporal focus</td>
<td>50%</td>
</tr>
<tr>
<td>Unifocal (vs bifocal)</td>
<td>45%</td>
</tr>
</tbody>
</table>
Primary effectiveness endpoint met
- 37.9% reduction in seizure frequency over the entire Blinded Period in stimulation group vs. 17% in sham group (p < 0.012, GEE)

- In final month of blinded period (month 4-5):
  - 42% vs 9% reduction in seizures (p=0.008)
Mean of Disabling Seizures by Month

Mean of Disabling Seizures by Month

Sham group receives stimulation

Treatment group receives stimulation

*GEE controlling for onset zone, number of seizure foci, and prior surgery
### RNS System Pivotal Trial: Responder Rates Over the Open Label Period

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Responder Rate, Total Disabling Seizures (%)</th>
<th>Open Label Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinded Eval Period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weeks 8-20</td>
<td>Weeks 20-32</td>
</tr>
<tr>
<td>Treatment</td>
<td>29.2% (28/96)</td>
<td>36.0% (67/186)</td>
</tr>
<tr>
<td>Sham</td>
<td>26.9% (25/93)</td>
<td>34.4% (63/183)</td>
</tr>
</tbody>
</table>
Pivotal Trial: Most Recent 12 Weeks of Open Label Period as of June 2010

Responder Rate: 50%
7% (13 subjects) Seizure Free

Each bar represents one subject
At 4 years post-implant: Mean seizure reduction > 50% reduction and responder rate > 50%
Pivotal Trial: Subset analyses

- No effect of prior surgery (1/3 had this) or VNS
- No effect of number of seizure foci (half had one, half had two)
- Possibly more effective with medial temporal onsets.
<table>
<thead>
<tr>
<th></th>
<th>Mesial Temporal Only</th>
<th>Other Foci</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>% change</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Treatment</td>
<td>48</td>
<td>-45%</td>
</tr>
<tr>
<td>Sham</td>
<td>47</td>
<td>-25%</td>
</tr>
</tbody>
</table>
Serious Adverse Events of Special Relevance: pivotal trial and all combined

- **Implant site infections**
  - Pivotal trial rate = 5% of subjects (9/191), 2% (4 patients) leading to explantation
  - All trials combined: 6% of subjects (15/256)
  - All infections were extradural

- **Intracranial Hemorrhage**
  - Pivotal trial and all combined: 4% of subjects
    - Only one with long-term sequelae (chronic headache)

- **Status epilepticus**
  - Rate = 3.5% subjects (9/256); 1.3 per 100 patient stimulation years
  - Episodes occurred between 5 months and 5 years post-implant
Deaths

• **SUDEP:** \(\leq 6\) cases = 6.3/1000 patient stimulation years
  – Literature based comparator 9.3 / 1000 patient years in epilepsy surgery candidates (Dasheiff et al 1991)
  – 2 deaths occurred while stimulation was off
  – One had “fatty infiltration of the right ventricle with fibrosis consistent with arrhythmogenic right ventricular dysplasia”

• 2 completed suicides **in 700 patient-years**
  – 1/350 patient-years or 3/1000 patient-years
  – Suicidality: 10% at baseline; 10-12% throughout study
    • (based on Beck Depression Inventory question)
Quality of Life and Neuropsychological Outcomes*

• There were statistically significant improvements in total and overall quality of life at 1 and 2 years
  – Also improvements in subscales of memory, language, attention/concentration, seizure worry, health discouragement, and work/social/driving function.

• The neuropsychological testing showed no deterioration in any measure at the end of the blinded evaluation period and at one and 2 years
  – There were statistically significant improvements at 1 and 2 years in some measures of learning, naming, verbal memory and visuospatial memory.

• 96% of patients elected to replace the battery
  – Current device average battery life: 3-5 years

* Personal communication, Dr. Martha Morrell, Neuropace, Inc.
Other uses of chronic, intracranial ambulatory EEG recordings

- Seizure prediction/warning/alarms
- Seizure awareness and seizure counting
  - Assessing efficacy of treatments
- Circadian, catamenial and other patterns, both interictal and ictal
- Lateralization of bitemporal seizures
- Many more…
Emily: College student, refractory bitemporal epilepsy
### MONTH BY DAY HISTOGRAM

<table>
<thead>
<tr>
<th>Color</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>Pattern A, Ch1(A1 - A2) Band Pass: 4-125 Hz, 10%, 4/8 + Line Length: 50%, 1s, 2m</td>
</tr>
<tr>
<td>Green</td>
<td>Pattern A, Ch2(B1 - B2) Off</td>
</tr>
<tr>
<td>Yellow</td>
<td>Pattern B, Ch1(A1 - A2) Off</td>
</tr>
<tr>
<td>Orange</td>
<td>Pattern B, Ch2(B1 - B2) Band Pass: 4-125 Hz, 10%, 8/16 + Line Length: 63%, 1s, 2m</td>
</tr>
<tr>
<td></td>
<td>No Data Available</td>
</tr>
</tbody>
</table>

The histogram shows data on the days of the month, with different colors indicating various patterns and measurements.

- **January 2000**:
  - L>R
  - R
  - L>R

- **December 2000**:
  - L>R
  - R
  - L
Wada: Right Injection
After right hippocampal resection

- No right side seizures or spikes after, including no spread.
- Still clusters from left, though she is unaware of any discrete seizures now
- Seizure “warning” system in place to treat clusters early and aggressively
- Got B’s in most classes this semester despite all of this
Seizure anticipation/prediction

Epileptiform activity per hr

Pt 1: 2 days prior to LE \( \geq 20 \) seconds

Seizure

Courtesy of Christopher Anderson, MD
Seizure anticipation/prediction

Epileptiform activity per hr

pt 4: 4 days prior to long episodes ≥ 20 seconds

Seizure

Courtesy of Christopher Anderson, MD
Room for improvement regarding efficacy

- There is much to learn about networks, targets, stimulation parameters including responsive or scheduled (or both).
- "Safety measures" and other trial limitations
  - Only 5 stimulations per episode
  - No scheduled stimulation
  - No continuous stimulation
Need for >5 stims/episode, I of III
Need for >5 stims/episode, II of III
Need for >5 stims/episode, III of III
Conclusions

- The era of brain stimulation is here, although still in its infancy
- Responsive neurostimulation was safe, well tolerated, effective (though not as effective as we’d like), and improved QOL
- The potential uses of a permanently implanted device that can record and interpret EEG are vast, including improving safety and quality of life, and potentially coupling with other types of treatment (drug delivery, cooling, etc)
The End