Neuromodulation in Dravet Syndrome

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What is neuromodulation?

- Seizures are caused by synchronized firing of an inappropriate network of neurons.
- Electrical current can be used to suppress neuronal firing or interfere with synchronized firing of a population of neurons.
- Electrical stimulation of the central nervous system in order to prevent seizures.
Open Loop vs. Closed Loop

**Open Loop:**
- Therapy delivered using pre-programmed settings
- Unaffected by changes in clinical symptoms

**Closed Loop:**
- Therapy delivered using pre-programmed settings
- Therapy modulated in response to physiologic changes
Open vs. Closed Loop

**Open Loop**
- Traditional Vagus Nerve Stimulation
- Deep Brain Stimulation
- Transmagnetic Stimulation

**Closed Loop**
- Cardiac Responsive Vagus Nerve Stimulation (Aspire)
- Responsive Neurostimulation (Neuropace)
Vagal nerve stimulation (VNS)

- Generator delivers intermittent electrical stimulus to wire coiled around left vagus nerve in neck

- Vagal nerve then transmits signal to the brainstem and then to areas involved in epileptogenesis.*
VNS mechanism of action

- Vagus nerve innervates nucleus tractus solitarius which innervates locus coeruleus, parabrachial nucleus, thalamus.

- VNS causes increased synaptic activity in thalamo-cortical projection which may decrease synchrony of synaptic activity between and within cortical regions.

- Decreased synaptic activity in components of the limbic system.

- Increased release of norepinephrine and serotonin.

Beekwilder, Beems 2010
Common to Neuromodulation Trials: An Induction Effect

Seen In Every Major Clinical Trial Of Neuromodulation For Epilepsy

Vagus Nerve Stimulation

RNS

Median Reduction in Seizures

<table>
<thead>
<tr>
<th>Time</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
<th>40%</th>
<th>45%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of RCT</td>
<td>23%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6 months</td>
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<td></td>
<td>34%</td>
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<tr>
<td>12 months</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>45%</td>
</tr>
</tbody>
</table>

Mean seizure count per month

Pre-implant Period (3 months)

Treatment: n=87
Sham: n=44

Blinded Evaluation Period

Open Label Period

Courtesy of CM DeGioigio
Challenges with efficacy in long-term VNS studies

- Difficult to assess long-term response to VNS.
  - Medication changes are common.
  - New AEDs may be added.

- Long term RCTs could be unsafe – increase risk of SUDEP in placebo or sham arm

Courtesy of CM DeGioigio
Randomized 112 adults with focal epilepsy to VNS plus best medical practice or best medical practice.

Allowed to change AEDs as needed.

At 12 months, responder rate 32% VNS vs. 24% best medical practice.
Most effective dose

- Data from 4 studies demonstrate 1.73 times more likely to achieve ≥50% seizure reduction with high current.

- Duty cycle (DeGiorgio 2005) – No significant difference between rapid, medium, and slow cycle.
### McHugh’s Classification of VNS Outcome

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>IA</th>
<th>IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>80-100% reduction in seizure frequency</td>
<td>Improved ictal or postictal activity</td>
<td>No improvement in ictal or postictal activity</td>
</tr>
<tr>
<td>Class II</td>
<td>50-79% reduction in seizure frequency</td>
<td>Improved ictal or postictal activity</td>
<td>No improvement in ictal or postictal activity</td>
</tr>
<tr>
<td>Class III</td>
<td>&lt;50% reduction in seizure frequency</td>
<td>Improvement in ictal or postictal activity</td>
<td>No improvement in ictal or postictal activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Magnet benefit only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>No benefit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VNS efficacy for Children

  - 347 Children (6 mo-18 y.o.)
  - Observed in 11 European centers over 24 months.
Orosz (continued)

- ≥50% reduction – 32.5% at 6 months, 43.8% at 12 months.

- Seizure severity decrease 34-42% of patients.

- Clinical Global Impression (“much improved” or “very much improved”) – 30% of patients at 12,24 month. Improvements in seizure duration, severity, and quality of life.
What dose is most effective?

- Mean output current 1.8mA from 12-24 months. Pulse width and signal frequency unchanged.
- Total charge delivered per day function of output current, pulse width, pulse frequency, on time, and off time.
- Significant difference b/w responders and non responders at 6 and 12 months. No significant difference at 24 months.
Orosz (continued)

- Dravet Subset:
  - 20 patients (age unknown)
    - Responder rates:
      - 25% (5/20) at 6 months,
      - 38.5% (5/13) at 12 months. (vs. 43.% of total cohort)
Fulton SP (AES 2015)

- 12 patients, 9/12 had >50% reduction in generalized tonic-clonic seizures, 2 were seizure-free after 1 year post-implant.

- Of the 9/12, 4 had significant improvement in cognition.

- No clear differences with rapid vs. intermediate vs. standard cycling.
Clinical course of young patients with Dravet syndrome after vagal nerve stimulation

Nelia Zamponi*, Claudia Passamonti, Silvia Cappanera, Cristina Petrelli

- 8 patients (5-25 y.o.)
- Goal parameters 2mA, 30hz, 5min off, 30 sec on
- Mean reduction – 6% at 6 months, 31% at 12 months.
- 5/8 had at least 33% reduction, 4/8 had at least 50% reduction

### Table 3 – Clinical data at the time of VNS implantation and outcome at 12 months follow-up.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Seizure types at implant</th>
<th>Presence of SE at implant</th>
<th>Cognitive Level at implant</th>
<th>Age at VNS implant (years)</th>
<th>No of seiz./month at baseline</th>
<th>No of seiz./month after 12 months</th>
<th>Seizure reduction after 12 months</th>
<th>McHugh’s Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GTC + MS</td>
<td>–</td>
<td>MMR</td>
<td>10</td>
<td>180</td>
<td>70</td>
<td>-61%</td>
<td>IIIB</td>
</tr>
<tr>
<td>2</td>
<td>GTC</td>
<td>–</td>
<td>SMR</td>
<td>25</td>
<td>15</td>
<td>10</td>
<td>-33%</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>GTC</td>
<td>+</td>
<td>mMR</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>0%</td>
<td>V</td>
</tr>
<tr>
<td>4</td>
<td>GTC</td>
<td>+</td>
<td>SMR</td>
<td>13</td>
<td>4</td>
<td>4</td>
<td>0%</td>
<td>V</td>
</tr>
<tr>
<td>5</td>
<td>GTC + MS</td>
<td>–</td>
<td>SMR</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>-50%</td>
<td>IIIB</td>
</tr>
<tr>
<td>6</td>
<td>GTC + MS</td>
<td>–</td>
<td>SMR</td>
<td>5</td>
<td>15</td>
<td>7</td>
<td>-53%</td>
<td>IIIB</td>
</tr>
<tr>
<td>7</td>
<td>GTC + CPS + MS</td>
<td>+</td>
<td>mMR</td>
<td>8</td>
<td>200</td>
<td>200</td>
<td>0%</td>
<td>V</td>
</tr>
<tr>
<td>8</td>
<td>CPS</td>
<td>–</td>
<td>MMR</td>
<td>9</td>
<td>10</td>
<td>5</td>
<td>-50%</td>
<td>IIIB</td>
</tr>
</tbody>
</table>

SE: Status Epilepticus; GTC: generalized tonic–clonic seizures; MS: Myoclonic seizures; CPS: complex partial seizures; mMR: mild mental retardation; MMR: moderate mental retardation; SMR: severe mental retardation; +: positive; –: negative.
Retrospective chart review of 15 patients.

Seizure frequency judged as improved, unchanged, or worsened.

3 DS (>3 y.o.) – all 3 had improved seizure frequency at 12 months.

No statistically significant association between parameters and seizure improvement.
VNS Aspire 106 (2015)

- Cardiac-based algorithm to detect heart-rate increase and deliver automatic stimulation.
Over 80% of patients have seizures associated with ictal tachycardia (55% increase in heart rate).

Heart rate change from baseline (previous 5 minutes of R-R intervals).

Seizure Detection Algorithm (SDA)—delivers stimulation when heart rate increases above threshold for 1s (≥20%, ≥40%, ≥60%).
A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation

- **1st** EMU Aspire clinical trial, 31 subjects
- Closed loop turned off, evaluating seizures
- Evaluating how seizures respond to SDA in patients with ictal tachycardia.
- SDA Randomized.
- 3-5 day observation in EMU after implant.

<table>
<thead>
<tr>
<th>Number of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure total</td>
</tr>
<tr>
<td>Seizures that could be observed for detection</td>
</tr>
<tr>
<td>≥20% increase in heart rate</td>
</tr>
<tr>
<td>Heart rate change &lt;20%</td>
</tr>
<tr>
<td>Heart rate change below randomized SDA</td>
</tr>
<tr>
<td>VNS triggered</td>
</tr>
<tr>
<td>Overlap between VNS trigger and seizure</td>
</tr>
<tr>
<td>Seizures stopped during stimulation</td>
</tr>
</tbody>
</table>
20 subjects implanted and studied in EMU

- 89 seizures captured
  - 31/89 seizures treated by automatic stimulation
  - 19/89 (21%) of all seizures were aborted by cardiac-based VNS
  - 61% of seizures treated were aborted.

### Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance—The U.S. E-37 Trial
Chronic electrical stimulation applied directly into deep nuclei in the brain.
Many animal epilepsy models involve the Circuit of Papez.

Interruption of this circuit prevents seizures.

The anterior portion of the thalamus is part of this circuit.
Stimulation of anterior nucleus of thalamus

**SANTE** (double-blinded, placebo-controlled) – 110 patients with partial seizures. 2010

- 3 months: 40.4% median decrease vs. 13.5%.
- 2 years (unblinded): 56% median reduction with 54% have a >50% seizure reduction.
- 5 years later, >50% seizure reduction rate 69% and median seizure reduction rate also 69%.
Centromedian (CM) nucleus
thalamic stimulation

- CM is part of the reticulothalamocortical system that is related to the modulation of the sleep-wake cycle and general alertness.
- Neurons from brainstem communicates with the thalamus and then sends signals throughout cerebral cortex.
- High frequency stimulation demonstrates EEG desynchronization in animal studies.
2 patients implanted prior to diagnosis

19 y.o.: AN implant, initial reduction of 81% of GTCs, 10 years later 98% reduction.

34 y.o.: CM implant, no seizure change for 2 years, CM electrodes disconnected and AN implanted, no change up to 5 years after implant. Over 10 years of treatment, reduced to 67-93% reduction per month.
5 patients between 5-38 y.o implanted.

1 patient with Dravet with STN nucleus implant at 19 y.o.

41.5% mean reduction in seizure frequency (follow up at 27 months).
External stimulation
Transcutaneous VNS

- Aihua, L; et al. 2014
  - Stimulate auricular branch of vagus nerve.
  - Randomized 60 patients by stimulation zone (Ramsay-Hunt vs. earlobe) for 12 months with no change in AEDs.
  - Treatment group: 40% reduction in seizure frequency vs. 0.85%. 
Transcutaneous VNS and Dravet – 2015
Clinical Neurophysiology Society Meeting

- Finetti, et. Al
  - 10 y.o. – 4 hours daily stimulation
  - 4 months later (no change in AED): 57% reduction in seizures.
Trigeminal stimulation

- Trigmenial nerve = 5th cranial nerve.
- Responsible for sensation of the face/head.
- Sends back signals to the brainstem which then transmits signals to thalamus and cortex.
Trigeminal stimulation

- External and subcutaneous devices.

- Phase 2 study - 2013 (DeGiorgio) – 12 hours/day, external device.

- 50 patients randomized control, 18 weeks.
Trigeminal stimulation efficacy

- >50% seizure reduction in 40.5% treatment group.
- >50% seizure reduction between treatment and control not significant (likely due to small number of patients).
- Side effects: skin irritation (14%), headache (4%), anxiety (4%)
Final thoughts and future possible directions

- Signals of efficacy of neuromodulation.
- Seizure reduction rates may be less in the Dravet population.
- Studies needed to develop Best Practice Guidelines.
- Dravet VNS studies
  - Multicenter
  - Utilizing REN registry
  - Compare traditional vs. cardiac
- Other neuromodulation studies pending FDA approval of devices.