Clinical Area: Epilepsy
Keywords: Epilepsy, Treatment, Vagus Nerve Stimulation

Study Type: Randomized multicenter controlled trial (active control)

Outcomes
• Primary: Total Seizure Frequency, Partial Onset Seizure Frequency
• Secondary: Global evaluation of well being, safety, side effects

Design
• N = 254
• Description of population: recruited from neurology clinics at 20 sites in the US
• Inclusion criteria: medically refractory partial onset seizures >6 seizures in 30 days current use of 1-3 anti-epileptic medications
• Exclusion criteria prior resective brain surgery significant comorbidity prior brain or vagal stimulation
• Power: 100 patients per group to detect a difference in mean primary outcome of 15% with 80% power and alpha set at 0.05
• Method of randomization: blinded in groups of 4 patients: 2 high and 2 low stimulation
• Intervention: Vagal Nerve Stimulation via NeuroCybernetics Prosthesis
  Low Stimulation Group (n=103)
  30 sec every 3 hours 130 microsecond pulses @ 1Hz
  mean age=34
  44 male:59 female
  High Stimulation Group (n=95)
  30 sec every 5 min 500 microsecond pulses @ 30 Hz
  mean age=32
  49 male:46 female

• Blinding: device turned off prior to each assessment patients not told about stimulation parameters, advised not to discuss stimulation frequency
• Length of follow-up: 4 months from time of randomization
• Completeness of follow-up: identified 254
  completed study 194 (76%)
Validity

• Is the study type appropriate for the questions being asked? Yes
• Was the study population typical of patients with this disease? Yes
• Were the treatment/control groups comparable at baseline? Yes
• Was the intervention compared to placebo and/or best accepted intervention? Yes
• Was there compliance with the intervention? Yes
• Was there equal intensity of observation of study and control subjects? Yes
• Was the process of observation likely to effect the outcome? No
• Intention to treat analysis? Yes
• Did conclusions about safety take into account the limited size of the study? Yes

Conclusions regarding validity of methods: Study is appropriately designed.

Results:

<table>
<thead>
<tr>
<th>Stimulation Parameter</th>
<th>Seizure Frequency at Baseline</th>
<th>Seizure Frequency with Stimulation</th>
<th>Absolute Risk Reduction</th>
<th>Relative Risk Reduction</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>7/week</td>
<td>6/week</td>
<td>1/week</td>
<td>15%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High</td>
<td>11/week</td>
<td>8/week</td>
<td>3/week</td>
<td>28%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*-within group

Safety-
- left vocal cord paralysis 2
- lower facial muscle paresis 2
- fluid around VNS 1

Morbidity—occurred only during stimulation
- voice alteration 30% 60%
- cough 43% 45%
- pharyngitis 25% 35%
- pain 30% 28%

Clinical Effect
In this study, vagal nerve stimulation as shown to produce a clinically and statistically significant reduction of between 1 and 3 seizures per week and improvements in perceived well being. The most common side effects were voice alteration and cough during stimulation. Although patients had the ability to terminate stimulation at any time, there was no report in this study that lack of effect or perceived harms resulted in patients turning off the VNS device.

Authors’ Conclusions:
Vagal nerve stimulation is an effective and safe adjunctive treatment for patients with refractory partial-onset seizures. It represents the advent of a new non-pharmacologic treatment for epilepsy.

Reviewers’ Conclusions: A well designed study demonstrating that vagal nerve stimulation produces a dose dependent clinically significant reduction in mean seizure frequency and a clinically significant improvement in perceived well being.