Alternative Treatments: Neuromodulation Approaches to Treatment Resistant Depression

Audrey R. Tyrka, MD, PhD
Assistant Professor
Brown University Department of Psychiatry
Associate Chief, Mood Disorders Program
Butler Hospital
Providence, Rhode Island
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant:</td>
<td>None</td>
</tr>
<tr>
<td>Full-time Employee:</td>
<td>None</td>
</tr>
<tr>
<td>Grant/Research Support:</td>
<td>Cyberonics; Department of Defense; Medtronic; National Institutes of Health (NIH); Neuronetics; Pfizer Inc; Sepracor; UCB Pharma</td>
</tr>
<tr>
<td>Continuing Medical Education Honoraria</td>
<td>Lundbeck, Takeda</td>
</tr>
<tr>
<td>Major Stockholder:</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial/ Material Interest:</td>
<td>None</td>
</tr>
</tbody>
</table>
Overview

- Electroconvulsive therapy (ECT)
- Magnetic seizure therapy (MST)
- Repetitive transcranial magnetic stimulation (TMS)
- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS)
- Considerations for new/experimental treatments
Electroconvulsive Therapy (ECT)

- Developed in 1930s, FDA-approved in 1979
- Patient under anesthesia
- 6 to 12 treatments (2-3/wk),
- Brief electrical pulse passed through scalp produces seizure on EEG
- Muscle paralysis prevents convulsive movement
Electroconvulsive Therapy (ECT)

- Considered the “gold standard” for severe depression

- Used for other severe disorders including mania, schizophrenia, and catatonia

- Often administered in the inpatient setting (hospitalized for 2-4 weeks)

- Can also be administered as an outpatient in some settings
Electroconvulsive Therapy (ECT)

- Treatment parameters influence the efficacy and tolerability of ECT.
- Bilateral appears more effective than unilateral treatment.
- Relatively higher doses of stimulation more effective.
- However, higher doses and bilateral treatments associated with more cognitive side effects, particularly in elderly individuals.
# Electroconvulsive Therapy vs. SHAM

<table>
<thead>
<tr>
<th>Trial</th>
<th># of Participants</th>
<th>Standard Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson, 1963</td>
<td>12</td>
<td>-1.078 (-2.289 to 0.133)</td>
</tr>
<tr>
<td>West, 1981</td>
<td>25</td>
<td>-1.255 (-2.170 to -0.341)</td>
</tr>
<tr>
<td>Lambourn, 1978</td>
<td>40</td>
<td>-0.170 (-0.940 to 0.600)</td>
</tr>
<tr>
<td>Freeman, 1978</td>
<td>40</td>
<td>-0.629 (-1.264 to 0.006)</td>
</tr>
<tr>
<td>Gregory, 1985</td>
<td>69</td>
<td>-1.418 (-2.012 to -0.824)</td>
</tr>
<tr>
<td>Johnstone, 1980</td>
<td>70</td>
<td>-0.739 (-1.253 to -0.224)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>-0.911 (-1.180 to -0.645)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>-0.908 (-1.270 to -0.537)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

## Effects of ECT vs. Pharmacotherapy

<table>
<thead>
<tr>
<th>Trial*</th>
<th># of Participants</th>
<th>Standard Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner, 1978</td>
<td>12</td>
<td>0.369 (-0.840 to 1.578)</td>
</tr>
<tr>
<td>Wilson, 1963</td>
<td>12</td>
<td>-0.513 (-1.663 to 0.637)</td>
</tr>
<tr>
<td>Davidson, 1978</td>
<td>19</td>
<td>-1.389 (-2.449 to -0.328)</td>
</tr>
<tr>
<td>McDonald, 1966</td>
<td>22</td>
<td>-0.930 (-1.813 to -0.047)</td>
</tr>
<tr>
<td>Gangadhar, 1982</td>
<td>32</td>
<td>1.287 (0.406 to 2.169)</td>
</tr>
<tr>
<td>MacSweeney, 1975</td>
<td>27</td>
<td>-0.714 (-1.492 to 0.065)</td>
</tr>
<tr>
<td>Dinan, 1989</td>
<td>30</td>
<td>-0.196 (-0.926 to 0.534)</td>
</tr>
<tr>
<td>Janakiramaiah, 2000</td>
<td>30</td>
<td>-1.095 (-1.863 to -0.328)</td>
</tr>
<tr>
<td>Folkerts, 1997</td>
<td>40</td>
<td>-1.336 (-2.032 to -0.640)</td>
</tr>
<tr>
<td>Herrington, 1974</td>
<td>43</td>
<td>-1.497 (-2.174 to -0.821)</td>
</tr>
<tr>
<td>Stanley, 1962</td>
<td>47</td>
<td>-1.342 (-2.047 to -0.638)</td>
</tr>
<tr>
<td>Medical Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Council, 1965</td>
<td>204</td>
<td>-0.559 (-0.883 to -0.234)</td>
</tr>
<tr>
<td>Greenblatt, 1964</td>
<td>242</td>
<td>-1.683 (-2.020 to -1.346)</td>
</tr>
</tbody>
</table>

Pooled fixed effects: -1.010 (-1.170 to -0.856)
Pooled random effects: -0.802 (-1.290 to -0.289)

*Other trials are not included: Kendrick, 1965; Bruce, 1960; Bagadia, 1981; Hutchinson, 1963; Robin, 1962

ECT Limitations

- Headache, jaw ache, soar throat muscle aches
- Cognitive side effects: memory
- Access: hospital, often inpatient
- Anesthesia risks
- Cost (generally covered by insurance)
- Maintenance (30%-84% of those who remit experience relapse in 6 months)
Magnetic Seizure Therapy (MST)

- Investigational
- Magnet-induced stimulus (like TMS)
- High intensity
- Target “antidepressant regions”
- Fewer side effects than ECT
- 3 sessions/week
- Same as ECT
  - Anesthesia
  - Tonic-clonic seizure
  - Monitor EEG, vital signs

This information concerns a use that has not been approved by the US Food and Drug Administration.
**MST: Shorter Period of Post-Ictal Disorientation and Inattention**

**Median Time (min) to Recover Full Orientation**

<table>
<thead>
<tr>
<th></th>
<th>MST</th>
<th>ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threshold</strong></td>
<td><img src="Threshold.png" alt="Graph" /></td>
<td><img src="ECT.png" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Suprathreshold</strong></td>
<td><img src="Suprathreshold.png" alt="Graph" /></td>
<td><img src="Suprathreshold.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

*Threshold MST vs ECT, $p<0.004$


*This information concerns a use that has not been approved by the US Food and Drug Administration.*
Recent FDA approval

Patient sits in chair and has treatment coil positioned on head (target site left dorsolateral prefrontal cortex)

40 min daily for 4-6 wks

Strong, pulsed magnetic fields pass through skull and produce small electrical currents in the brain that can activate brain cells
Potential Advantages of TMS

- No anesthesia
- Most common side effects are scalp pain or discomfort, particularly in the first week
- No systemic side effects such as cognitive effects, weight gain, sexual dysfunction, gastrointestinal
- Greater control over site
TMS Limitations

• Device approved by FDA for those with only one treatment

• Optimal stimulation parameters?

• Maintenance Treatment?

• 5 days/week for 4 to 6 weeks

• High Cost; will this be covered by insurance companies?
Neuronetics TMS Trials: Patient Criteria

• Male or female outpatients with major depressive episode, of moderate to severe symptom severity

• Baseline HAM-D 17 total score > 20, Item 1 > 2

• Treatment resistance defined by lack of response to at least one and no more than four antidepressant treatments in current episode

• Duration of current episode ≤ 3 years

• Clinically appropriate to discontinue existing antidepressant medications. Off antidepressants for the TMS trial.
TMS Acute Study Outcomes

A. MADRS (p=.058)

B. HAMD17 (p=.005)

O’Reardon et al, 2007

*Biological Psychiatry*
TMS Response and Remission Rates in Neuronetics Acute Study

**A** MADRS Response Rates (50% Improvement from Baseline)

- Week 2: 8.4, 6.2
- Week 4: 18.1, 11.0
- Week 6: 23.9, 12.3

**B** HAMD17 Response Rates (50% Improvement from Baseline)

- Week 2: 11.6, 8.9
- Week 4: 26.6, 11.6
- Week 6: 24.5, 13.7

**MADRS Remission Rates (MADRS Total Score < 10)**

- Week 2: 3.9, 2.1
- Week 4: 7.1, 6.2
- Week 6: 14.2, 5.5

**HAMD17 Remission Rates (HAMD17 Total Score < 8)**

- Week 2: 3.2, 2.1
- Week 4: 7.1, 6.2
- Week 6: 18.5, 8.9

* P < .05 vs sham, ** P < .01 vs sham

O’Reardon et al, 2007 *Biological Psychiatry*
Highly Significant Outcomes in Subset (n=164) who did not respond to ONE Adequate Antidepressant Trial

MADRS Total Score
(Baseline to Endpoint Change)

HAMD24 Total Score
(Baseline to Endpoint Change)

Lisanby SH et al, Biological Psychiatry 2008
Meta-Analysis of the Antidepressant Efficacy of High-Frequency rTMS

- 30 double-blind sham-controlled studies
- n=1164
- Overall Effect Size 0.39
- p < 0.0001
- No difference between med-resistant and non med resistant depression

Schutter, Psychological Medicine, 39, 65-75, 2009
Sequential Right- and Left-Sided Adjunct TMS

- TMS added to medication treatment
- Patients who had not responded to 2 adequate trials of medication
- Dorsolateral Prefrontal Cortex

Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy in 1997
- FDA approved for Treatment Resistant Depression in July 2005
- Implanted in over 30,000 patients worldwide
- Pulse generator implanted in left chest wall, wire attached to left vagus nerve in the neck
- Mild electrical pulses to the vagus nerve for transmission to the brain
Vagus Nerve Stimulation (VNS)

- Intermittent stimulation
  - 30 s on/5 min off
  - 24/7 continuous cycles

- Simple in-office programming (dosing) by treating physician

- Patient provided with Magnet that can turn VNS off

- No known interactions with medications
# Studies Into Potential Mechanism of Action of VNS Therapy

## DEPRESSION

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Method</th>
<th>Subjects</th>
<th>Time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Dorr</td>
<td>Surgery</td>
<td>Rats</td>
<td>1 h–3 mo</td>
<td>VNS associated with progressive increases in firing rates</td>
</tr>
<tr>
<td>2005</td>
<td>Zobel</td>
<td>SPECT</td>
<td>Humans</td>
<td>4 mo</td>
<td>rCBF changes in VNS Therapy were similar to previously noted changes in SSRIs</td>
</tr>
<tr>
<td>2004</td>
<td>Carpenter</td>
<td>CSF</td>
<td>Humans</td>
<td>2 wk–6 mo</td>
<td>Significant increase in HVA but not in other CSF concentrations</td>
</tr>
<tr>
<td>2003</td>
<td>Kling</td>
<td>Labeling</td>
<td>Rats</td>
<td>90 min</td>
<td>Fos labeling after VNS was greater than controls in several brain stem regions</td>
</tr>
<tr>
<td>2003</td>
<td>Hagen</td>
<td>PET</td>
<td>Humans</td>
<td>7–10 d, 12 mo</td>
<td>Metabolic decreases in hypoactive, ventral brain regions in VNS Therapy responders</td>
</tr>
<tr>
<td>2002</td>
<td>Devous</td>
<td>SPECT</td>
<td>Humans</td>
<td>10 wk</td>
<td>VNS Therapy improved rCBF in dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>2002</td>
<td>Conway</td>
<td>FDG PET</td>
<td>Humans</td>
<td>3 mo, 24 mo</td>
<td>Acute and chronic metabolic increases in different brain regions</td>
</tr>
<tr>
<td>2001</td>
<td>Bohning</td>
<td>fMRI</td>
<td>Humans</td>
<td>2 wk–23 mo</td>
<td>BOLD response to VNS Therapy found in brain regions affected by vagus nerve</td>
</tr>
</tbody>
</table>

## EPILEPSY

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Method</th>
<th>Subjects</th>
<th>Time</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Dean</td>
<td>TMS</td>
<td>Humans</td>
<td>6–12 mo</td>
<td>VNS Therapy altered motor cortex excitability</td>
</tr>
<tr>
<td>1999</td>
<td>Henry</td>
<td>PET</td>
<td>Humans</td>
<td>3 mo</td>
<td>rCBF increases in right/left thalami correlated with reduction in seizure frequency</td>
</tr>
<tr>
<td>1998</td>
<td>Henry</td>
<td>PET</td>
<td>Humans</td>
<td>3 mo</td>
<td>rCBF increased and decreased in different structures</td>
</tr>
<tr>
<td>1992</td>
<td>Hammond</td>
<td>CSF</td>
<td>Humans</td>
<td>2 mo</td>
<td>CSF changes correlated with reduction in seizure frequency</td>
</tr>
</tbody>
</table>
VNS Pivotal Study Design

Treatment Group

Fixed “Dose” VNS

Stimulation adjustment

2 weeks

8 weeks

Long-Term Phase

Sham-Control

Implant

Baseline

Up to 45 days before implant

Recovery and randomization

2 weeks

# VNS Pivotal Study: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Patient and Disease Characteristics</th>
<th>Treatment (n=112)</th>
<th>Sham-Control (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis: unipolar/bipolar</td>
<td>88%/12%</td>
<td>91%/9%</td>
</tr>
<tr>
<td>Average duration illness, lifetime/current episode (years)</td>
<td>26.1/3.9</td>
<td>24.9/4.3</td>
</tr>
<tr>
<td>Number of lifetime episodes of depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>61%</td>
<td>54%</td>
</tr>
<tr>
<td>6-10</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>% treated with ECT, current episode/lifetime</td>
<td>33%/51.8%</td>
<td>38.2%/53.6%</td>
</tr>
<tr>
<td>Average # previous unsuccessful treatments, current episode</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Baseline HAMD_{24}</td>
<td>28.8</td>
<td>29.7</td>
</tr>
</tbody>
</table>

Acute VNS Pivotal Study Results: LOCF 12-Week Response Rates

HAMD$_{24}$ (Primary Outcome)
IDS-SR$_{30}$ (Secondary Outcome)

VNS Pivotal Study Design

Treatment Group

- Stimulation adjustment
- 2 weeks
- Fixed “Dose” VNS
- 8 weeks
- Long-Term Phase

Sham-Control

Long-Term Phase (2 years)

This graph reports the available population for each assessment at each visit. Montgomery-Åsberg Depression Rating Scale (MADRS) data not available for 24-month group.

## Adjunctive VNS vs Treatment as Usual: Comparison of Patient Populations

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>VNS + TAU (n=205)</th>
<th>TAU (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (yr)</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>% female</td>
<td>64%</td>
<td>69%</td>
</tr>
<tr>
<td>Baseline HAMD(_{24})*</td>
<td>28.0</td>
<td>27.5</td>
</tr>
<tr>
<td>Avg duration, lifetime illness (yr)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Avg duration, current episode (yr)</td>
<td>4.2</td>
<td>5.7</td>
</tr>
<tr>
<td>% treated with ECT, current episode</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Avg # failed adequate treatments, current MDE (ATHF)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*For patients with 12-month assessment.

TAU=treatment as usual.

*p*<0.001.

VNS Pivotal Study vs. Comparative Study (TAU): Primary Analysis

1-Year Scores by Month (Evaluable Population)

- IDS-SR$_{30}$ Score
- Comparative study (n=124)
- Pivotal study (n=205)

$p<0.001$

VNS vs TAU: 12-Month HAMD$_{24}$

12-Month HAMD$_{24}$ Response and Remission Rates
(Evaluable Patient Population; Observed Data)

VNS Longer-Term Adverse Events

*AEs are possibly, probably, or definitely related to stimulation based on observed cases.
†9-month follow-up corresponds to 1 year post-implant.
‡Statistically significant improvement from 3 months ($p \leq 0.01$).

VNS: Limitations

- Long term data not randomized
- Delayed antidepressant response
- Surgical procedure
- Cosmetic issues
- MRI contraindication
- Battery life (6-10 yr)
- Cost/insurance issues
Deep Brain Stimulation (DBS)

- FDA approved for Parkinson’s and tremor, and now OCD. Under study for Treatment-Resistant Depression

- MRI to locate the target, then surgical holes in skull for electrode placement

- Two chest-wall internal pulse generators

- Stimulation parameters programmed by computer, through “wand”

*This information concerns a use that has not been approved by the US Food and Drug Administration.*
DBS: Subcallosal Cingulate Region (n=20)

Lozano, et al., Biological Psychiatry, 64, 461-67, 2008
DBS of Ventral Anterior Limb Internal Capsule/Ventral Striatum (n=15)

DBS Nucleus Accumbens (n=3)

Schlaepfer et al, *Neuropsychopharmacology, 33*(2), 368-77, 2008
Deep Brain Stimulation Limitations

• Considerable surgical risk
• Cosmetic issues
• Battery life
• Limited, short-term, open-label data in psychiatry
• 2 Large Multi-center studies just recently started
• Optimal Targets and stimulation parameters?
• Future MRIs problematic
• Risk of hypomania

This information concerns a use that has not been approved by the US Food and Drug Administration.
The New Frontier: Neuromodulation of Treatment Resistant Depression

“I’m trying alternative magnet therapy. I wonder how many of these magnets you’re supposed to take.”