Alternative Treatments: Neuromodulation Approaches to Treatment Resistant Depression

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Disclosures

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>25-125</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>-0.929 (-1.284 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>

### Effects of ECT vs. Pharmacotherapy

#### 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

#### MST: Shorter Period of Post-Ictal Disorientation and Inattention

#### Transcranial Magnetic Stimulation (TMS)
- 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 and intensity of stimulation

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**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?

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**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 \( \leq \) 3 years

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

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**TMS Acute Study Outcomes**

**A. MADRS**

\( p = .058 \)

**B. HAMD17**

\( p = .005 \)

*O’Reardon et al, 2007*

*Biological Psychiatry*

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**TMS Response and Remission Rates in Neuronetics Acute Study**
Highly Significant Outcomes in Subset (n=164) who did not respond to ONE Adequate Antidepressant Trial

Meta-Analysis of the Antidepressant Efficacy of High-Frequency rTMS

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

VNS: Pathway to the Brain

Studies Into Potential Mechanism of Action of VNS Therapy

VNS Pivotal Study Design

VNS Pivotal Study: Baseline Patient Characteristics

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

VNS Pivotal Study Design

Long-Term Response VNS Pivotal Study

Adjunctive VNS vs Treatment as Usual: Comparison of Patient Populations
VNS Pivotal Study vs. Comparative Study (TAU): Primary Analysis

VNS vs TAU: 12-Month HAMD24

VNS Longer-Term Adverse Events

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”

DBS: Subcallosal Cingulate Region (n=20)

DBS of Ventral Anterior Limb Internal Capsule/Ventral Striatum (n=15)

DBS Nucleus Accumbens (n=3)

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

The New Frontier: Neuromodulation of Treatment Resistant Depression