The Emerging Role of Transcranial Magnetic Stimulation for Treatment of Depression

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  - AstraZeneca; Bristol-Myers Squibb; Janssen Pharmaceutica; Neuronetics

- **Speaker’s Bureau**
  - AstraZeneca; Bristol-Myers Squibb; Janssen Pharmaceutica; Neuronetics; Pfizer
Major Goals

- Better appreciate the need for alternative treatments to manage major depression
- Consider the role of **neuromodulation** for treatment of major depression
- Focus on the definition, administration and adverse effects associated with **transcranial magnetic stimulation**
Impact of Depression

- WHO predicts major depression will be ranked as second most disabling disease by 2020
- In the US, major depression is the second leading cause of disability in women 15-44 years of age
- Complex interrelationship with several medical comorbidities
Major Depression

14 Million Adults
U.S.

7.2 Million Treated

6.8 Million Untreated

3.2 Million Adequately Treated

4 Million Poorly Served

• Inadequate response
• Intolerant to side effects

Kessler RC; Berglund P; Demler O; et al. The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095-3105.
In MDD, “Adequate” Treatment Is Difficult to Achieve\textsuperscript{1-3}

Factors contributing to inadequate treatment include:

- Adequate Dosage
- Adequate Duration
- Lack of Efficacy
- Poor Tolerability
- Nonadherence
- Safety Issues
- Comorbidities

Therapeutic Neuromodulation

- Delivers electrical current to nervous tissue
- Based on concept of functional disturbances in distributed neuronal circuits
- Episodic impact on brain
- Usually no sustained systemic effects

Neuromodulation Techniques

SEIZURE
- Electroconvulsive Therapy
- Magnetic Seizure Therapy*
- FEAST*

NON-INVASIVE

NO SEIZURE
- Bright light therapy
- Transcranial Magnetic Stimulation
- Vagus Nerve Stimulation
- Deep Brain Stimulation*
- tDCS*

INVASIVE

*Not FDA approved.
Electroconvulsive Therapy

- Access/patient acceptance
- Optimal administration
- Relapse rates
- Adverse effects
  - Cognitive
- Cost
Vagus Nerve Stimulation

- **Efficacy**
  - May benefit TRD

- **Advantages**
  - Absence of adverse cognitive and psychomotor effects
  - Absence of antidepressant-related AEs or drug interactions
  - Improved adherence

- **Disadvantages**
  - Acute vs longer-term efficacy
  - Cost
Transcranial Magnetic Stimulation (TMS)
TMS: Definition

- **Pulsed magnetic fields** of ~1.5 Tesla in strength
- Magnetic fields **pass unimpeded** approximately 2–3 cm in depth
- Induces a **focal electrical current** in cortical tissue
- Produces **local and distal functional changes** in the target neural circuitry
## TMS: Evidence for Antidepressant Effect

<table>
<thead>
<tr>
<th></th>
<th>Meds</th>
<th>ECT</th>
<th>TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active in animal behavioral models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Porsolt forced swim test</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Active in animal biologic models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increases in brain monoamine turnover</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Induction of neurogenesis genes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Normalization of stress (HPA) axis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Active in human biologic models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normalization of stress (HPA) axis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Delay in REM latency (sleep)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Increases in RCBF and glucose metabolism in CNS mood circuitry</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Empirically effective in RCTs for the treatment of MDD</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

TMS: Therapy System

- **Electrical source**
- Large capacitors
- Magnetic **stimulator**
- **Cable** with minimal resistance
- Stimulating **coil**
- Computer **program**
  - produces a pattern of magnetic pulses over a brief timeframe
TMS: Stimulation Parameters

- Motor threshold (80–120%)
- Frequency (<1 Hertz; 1–20 Hertz)
- Stimulation train (2–5 sec)
- Intertrain intervals (5–60 sec)
- Coil configuration and placement
- Frequency of stimulation
  - Single versus repetitive (rTMS)
  - Slow versus rapid rTMS
TMS: Key Terms

- **Pulse Train**: group of electromagnetic pulses followed by non-pulse interval
- **Stimulation Time**: duration of pulse train, measured in seconds
- **Interval**: time period between pulse trains, measured in seconds

**Single Magnetic Pulse**

**Pulse Train** (10 pulses/sec)

**Treatment Session**

- Time: 4 sec, 26 sec, ~40 min
TMS: Meta-analysis of Early vs Later Studies

* Standardized mean difference between active and sham rTMS groups.
† NeuroStar TMS Therapy clinical trials not included in analysis.

Neuronetics TMS Study Design

- **Real** TMS versus **sham** procedure
- 301 treatment-refractory, unipolar **major** depressed subjects
- **Multi-site** trial (23 centers)
- **MADRS**, HAMD$_{17,24}$, IDS-SR 30, GGI-S

Neuronetics TMS Study Design

Randomized, Controlled Study1,2,4 ‘101’

Open-Label Crossover Study2,3,4 ‘102’

Improved

Maintenance of Effect Study2,4,5 ‘103’

Not Improved

Improved

Inclusion Criteria

- Male or female outpatients meeting DSM-IV diagnostic criteria for major depressive episode, single or recurrent, of moderate to severe symptom severity (CGI-S > 4)
- Baseline HAM-D 17 total score > 20, Item 1 > 2
  - Interim symptom severity criterion prior to randomization, HAMD 17 total score > 18, and < 25% decrease in total score from baseline
- Treatment resistance defined by failure to respond to at least one and no more than four antidepressant treatments in current episode
  - Using the Antidepressant Treatment History Form (ATHF)
- Duration of current episode ≤ 3 years
- Clinically appropriate to discontinue existing antidepressant

Neuronetics 2100 CRS™

Overall Efficacy

MADRS Total Score
(Baseline to Endpoint Change)

HAMD-24 Total Score
(Baseline to Endpoint Change)

* P<.05.
LOCF, LS mean.
MADRS Response and Remission Rates: Overall Population

MADRS Response Rates
(50% Improvement from Baseline)

MADRS Remission Rates
(MADRS Total Score <10)

* = Active TMS

** = Sham TMS

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

Efficacy in Indicated Population

MADRS Total Score (Baseline to Endpoint Change)$^1$

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active TMS</td>
<td>0</td>
<td>-6.5</td>
<td>-6.0</td>
<td>-4.5</td>
</tr>
<tr>
<td>Sham TMS</td>
<td>0</td>
<td>-6.2</td>
<td>-5.7</td>
<td>-4.3</td>
</tr>
</tbody>
</table>

** $P<.01$

LOCF analysis of evaluable study population.


HAMD-24 Total Score (Baseline to Endpoint Change)$^2$

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active TMS</td>
<td>0</td>
<td>-7.5</td>
<td>-6.0</td>
<td>-5.5</td>
</tr>
<tr>
<td>Sham TMS</td>
<td>0</td>
<td>-7.2</td>
<td>-5.7</td>
<td>-4.3</td>
</tr>
</tbody>
</table>

** $P<.01$

LOCF analysis of evaluable study population.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Active TMS (n=165) n (%)</th>
<th>Sham TMS (n=158) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Eye pain</td>
<td>10 (6.1)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Toothache</td>
<td>12 (7.3)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>General disorders and site-administration conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Application-site discomfort</td>
<td>18 (10.9)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>• Application-site pain</td>
<td>59 (35.8)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>• Facial pain</td>
<td>11 (6.7)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Muscle twitching</td>
<td>34 (20.6)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pain of skin</td>
<td>14 (8.5)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*Adverse events occurring in the active treatment group at a rate of \( \geq 5\% \) and at least twice the rate of sham.

Time Course for These Adverse Events

# Serious Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Sham (N=158)</th>
<th>Active (N=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>General disorders and site administration conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Application site pain</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>- Facial pain</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Burns, first degree</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>- Overdose (Operator error, Asymptomatic)</td>
<td>0</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Depression</td>
<td>3 (1.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>- Intentional self injury</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>- Suicidal ideation</td>
<td>3 (1.9)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*Acute Treatment Phase data shown*

Emergent Suicidal Ideation

*Shift Score indicates the percent of subjects who experienced a change in HAMD Item 3 score from 0 or 1 at baseline to 3 or 4 at later point in time.

Auditory Threshold

Neurocognitive Testing

All contrasts non-significant, $P > .05$

5 of 8 published trials reported antidepressant equivalence between TMS and ECT.

1 trial found UL ECT plus medication superior to TMS monotherapy in MDD with psychosis but comparable in efficacy to TMS for MDD without psychosis.

1 trial reported UL ECT to be superior to TMS.

1 trial reported BL ECT to be superior to TMS.

TMS versus ECT Study: HAMD$_{24}$ Scores

## TMS versus ECT Study: Response Rates

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>HAMD: ((\geq 50% \ &amp; \ 8))</th>
<th>HAMD: ((&lt;50% \ &amp; \ &gt;8))</th>
<th>TMS (n=17)</th>
<th>ECT (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>7</td>
<td>10</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Response Rate</td>
<td>41%</td>
<td>43%</td>
<td><strong>41%</strong></td>
<td><strong>43%</strong></td>
</tr>
</tbody>
</table>

Fisher’s Exact Test; p=ns

## TMS versus ECT Study: Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>TMS</th>
<th>ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse effects</strong></td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Mild adverse effects</strong></td>
<td>Facial twitching</td>
<td>Short-term memory impairment</td>
</tr>
<tr>
<td></td>
<td>Erythema at site of coil placement</td>
<td>Drowsiness shortly after treatment</td>
</tr>
<tr>
<td></td>
<td>Anxiety before and during treatment</td>
<td>Postictal and anesthesia-induced confusion</td>
</tr>
<tr>
<td></td>
<td>Localized to stimulation site:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild pain or discomfort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feelings of warmth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tapping sensation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
</tr>
</tbody>
</table>
TMS versus ECT Study: Neurocognitive Effects

- No evidence of adverse neurocognitive effects in our TMS-treated subjects.
- Further, preliminary analysis indicated improvement over baseline scores in some domains.
- This may be due to improved attention and concentration or practice effects.

TMS for Depression: Summary

- **TMS superior to sham TMS for MDD**
- **TMS may produce similar efficacy to ECT for more severe depression (5/8 trials were supportive)**
- **Serious adverse effects** (e.g., seizure, cognitive) with TMS are rare to absent

Major Goals

- Better appreciate the need for alternative treatments to manage major depression
- Consider the role of **neuromodulation** for treatment of major depression
- Focus on the definition, administration and adverse effects associated with **transcranial magnetic stimulation**
References I


