Clinical Applications of TMS & Evidence in Depression

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Overview

• TMS Basics in Psychiatry

• TMS studies in depression

• Treatment program at BIDMC
Disclosures

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Neosync (Clinical Trial Site PI)
Disclosures (cont.)

• TMS has been approved for treatment in treatment-resistant depression and OCD though we may discuss other uses which have not been FDA approved.

• Some portion of the material has been shared by other members of the BA-CNBS and are used with permission.

• I have no financial conflicts to report.
What is the need for non-invasive brain stimulation?

STAR*D Study (N=2,876)

- Remission: ~33%
- Mild symptoms: ~28%
- Moderate symptoms: ~23%
- Severe symptoms: ~12%
- Very severe symptoms: ~4%

Depressive Symptoms (QID-SR Score) After Up to 12 Weeks Antidepressant Treatment

STAR*D = Sequenced Treatment Alternatives to Relieve Depression
What about Electroconvulsive therapy (ECT)?

- Many decades of safety and efficacy data

- Gold Standard for treatment-resistant depression

- Invasive stimulation requiring anesthesia with frequent cognitive adverse effects

- Enormous stigma

Image courtesy of:
Electro-Magnetic Induction

“I think I got hold of a good thing”

M. Faraday
29 August 1831
Stimulation Coils
Topographic resolution
Figure 1. Transcranial magnetic stimulation coil placement over the dorsolateral prefrontal cortex and its connectivity to subcortical loops and associated functional neural networks, including the subgenual cingulate.

ACC: Anterior cingulate cortex; dIPFC: Dorsolateral prefrontal cortex; DL: Dorsolateral; LDM: Lateral dorsomedial; MD: Mediodorsal; NA: Nucleus accumbens; TMS: Transcranial magnetic stimulation; V: Ventral; VA: Ventral anterior; VM: Ventromedial.

Adapted with permission from [35].

Scalp to Brain Relation
TMS Parameters

Paradigm

- Single Pulse TMS (spTMS)
- 1 Hz rTMS
- 10 Hz rTMS
- Continuous Theta Burst (cTBS)
- Intermittent Theta Burst (iTBS)

Net Effect

- None
- Inhibitory
- Excitatory
- LTD-like
- LTP-like
rTMS: Lasting Modulation of Cortical Activity

Sham TMS

1 Hz TMS

20 Hz TMS

Valero et al. 2002
Therapeutic Applications of rTMS

- Depression
- Bipolar Disorder
- OCD
- PTSD
- Schizophrenia
- Pain
  - Visceral pain
  - Atypical facial pain
  - Phantom pain
- PD
- Focal dystonia
- Epilepsy
- Stuttering
- Tics
- Neurorehabilitation
  - Neglect
  - Aphasia
  - Hand weakness
Obsessive Compulsive Disorder (OCD) Treatment

BrainsWay introduces the First FDA Cleared (De-Novo) Non-invasive Medical Device for the Treatment of OCD

www.brainsway.com/treatments/obsessive-compulsive-disorder
Potential Adverse Effects

- **Common:**
  - Headache
  - Auditory effects

- **Rare**
  - Seizure induction
  - Effects on Cognition
  - Mania
  - Endocrine effects
rTMS in Depression

- Kolbinger et al. 1993, 95
- Grisaru et al. 1994
- George et al. 1996

- Pascual-Leone et al. 1996
  - Double Blind
  - Multiple Control Conditions
  - 17 patients
  - 9/17 with ∂HDRS > 50%

*Figure 1: Hamilton depression rating scale (HDRS) and Beck questionnaire (BQ) scores according to rTMS stimulation condition*

Symbols represent mean score (and SD) of raw scores for all 17 patients at baseline (weeks before first rTMS session), and at end of each week of rTMS session. Stimulation condition A=real left DLPFC stimulation; B=real right DLPFC stimulation (control); C=sham left DLPFC stimulation (control); D=sham right DLPFC stimulation (control); E=real vertex stimulation (C, control). Order of different stimulation conditions was randomised across patients. To generate these analyses, months of the same stimulation condition were arranged together, therefore, sequence A–E does not represent a real ordering in time.
rTMS for depression treatment
Efficacy - Review

Neuronetics - NeuroStar

- Treatment Coil
- Display
- Mobile Console
Sen-Star Treatment Link

4 key functions:

* Contact sensing to ensure treatment coil is positioned correctly
* Magnetic field confirmation to ensure patient receives desired treatment
* Surface field cancellation to reduce stimulation of the scalp
* Charge approximately $100 per treatment
Stimulation Parameters

10 pulses/sec
120% of motor threshold
3000 pulses/session
4–6 weeks
Iron-core coil
Study 101 Patient Population

● Diagnosis, Disease Severity & Illness Course
  - DSM-IV Diagnosis: Major Depressive Disorder
  - Largely (~95%) recurrent illness course
  - Approximately 50% unemployed due to illness
  - Moderate to severe symptom burden
    ▶ Avg HAMD24 ~30, MADRS ~32 at study entry

● Treatment Resistance
  - Moderate to severe treatment resistance in current episode
    ▶ Nearly 50% failed to receive benefit from >2 adequate treatments (ie, dose/duration)
    ▶ Nearly all received multiple (avg ≥ 4), ineffective treatments in current episode
# Comparison of TMS Study Population to ECT Reference Population

<table>
<thead>
<tr>
<th></th>
<th>Neuronetics Active TMS (N=155)</th>
<th>OPT-ECT Study (N=139)*</th>
<th>Community ECT Study (N=129)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● N(%) Female</td>
<td>86 (55.5)</td>
<td>95 (68.3)</td>
<td>82 (63.6)</td>
</tr>
<tr>
<td>● Age in years (SD)</td>
<td>47.9 (11.0)</td>
<td>46.8 (13.2)</td>
<td>48.2 (11.7)</td>
</tr>
<tr>
<td><strong>Clinical Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Recurrent illness course N (%)</td>
<td>149 (95.5)</td>
<td>110 (79.1)</td>
<td>84 (65.1)</td>
</tr>
<tr>
<td>● Duration of current episode in mos (median)</td>
<td>10.0</td>
<td>11.0</td>
<td>8.3</td>
</tr>
<tr>
<td>● N (%) with current episode &gt; 2 years</td>
<td>36 (23.2)</td>
<td>21 (15.1)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td><strong>Treatment History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● # Adequate in Current Episode</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Baseline Symptom Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● HAMD 24 total score (Mean [SD])</td>
<td>30.1 (5.0)</td>
<td>33.9 (6.7)</td>
<td>30.7 (6.6)</td>
</tr>
</tbody>
</table>

*Subset analysis provided by H. Sackeim
**Study 101 Trial Design**

*Randomized, Double-blind, Sham-Controlled*

**Phase I**
- Drug-Free Lead-In
- 7-10 days

**Phase II**
- **Acute Treatment Phase**
  - 6 weeks
- NeuroStar TMS Therapy
  - (N=155)
- Sham TMS
  - (N=146)

**Phase III**
- **Taper Phase**
  - 3 weeks
- [TMS Taper + Open-label AD Mono-Rx]

**Randomization**
- n=325

**Primary Timepoint @ 4 weeks**

**Secondary Timepoint @ 6 weeks**

**Durability of Effect @ 9 weeks**
Study 101 Efficacy Outcomes Continuous Measures

Pre-specified LOCF analysis of evaluable study population
Study 101: Significant Clinical Effects on HAMD Categorical Measures

**HAMD24 Response**
(≥50% Improvement from Baseline)

- **Week 4**: P = .030
  - Active: 19.4%
  - Sham: 11.6%

- **Week 6**: P = .042
  - Active: 23.9%
  - Sham: 15.9%

**HAMD24 Remission**
(HAMD Total Score < 11)

- **Week 4**: P = .644
  - Active: 7.1%
  - Sham: 6.2%

- **Week 6**: P = .012
  - Active: 17.4%
  - Sham: 8.2%
Acute Effects in Study 101 are Sustained
Maintained Effect in Taper From TMS to Pharmacotherapy

91.9% of Acute Phase Responders Persist Through End of Taper Phase

LOCF analysis of evaluable study population
Clinical Benefit Varies by Prior Treatment Failure in Both STAR-D and TMS Study 102

Comparison of Monotherapy Outcomes: Pharmacotherapy vs TMS

<table>
<thead>
<tr>
<th>Sample Size (N)</th>
<th>No or Limited Prior Rx</th>
<th>One Prior Failure</th>
<th>Two Prior Failures</th>
<th>Three Prior Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Remission (HAMD 17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2876</td>
<td>27.5%</td>
<td>25.6%</td>
<td>17.9%</td>
<td>18.2%</td>
</tr>
<tr>
<td>727 43</td>
<td>21.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221 28</td>
<td>16.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58 11</td>
<td></td>
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</tbody>
</table>

[Low] Treatment Resistance [High]
How does TMS compare to other approaches for treatment-resistant depression?

- Olanzapine/Fluoxetine (Thase, 2007): 0.33
- Aripiprazole (Marcus, 2008): 0.34
- Neurostar TMS Therapy (Demitrack, 2009): 0.52
- Brainsway DeepTMS (Levkovitz, 2015): 0.76
- Electroconvulsive Therapy (UK ECT Review Group, 2003): 0.91
Brainsway DeepTMS: A New Device
Over 900 phone screenings

Over 470 subjects excluded

428 consented

216 subjects excluded
Subjects did not meet eligibility criteria, withdrew consent or left the study before randomization

212 subjects (ITT sample)

31 subjects excluded
Subjects’ average stimulation intensity was <118% of measured MT

181 subjects (PP sample)

89 dTMS
- 7 dropouts (baseline-5 weeks) (7.9%)
- 82 subjects reached the primary endpoint
- 39 dropouts (6-16 weeks) (43.8%)
- 43 subjects completed the study

92 sham treatment
- 15 dropouts (baseline-5 weeks) (16.3%)
- 77 subjects reached the primary endpoint
- 49 dropouts (6-16 weeks) (53.3%)
- 28 subjects completed the study
DeepTMS HDRS Change

Levkovitz, et al. World Psychiatry 2015;14:64–73
Is this as good as it gets? Probably Not.

What about Stim. Target?
iTBS is just as effective?

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yeshiho Noela, Peter Giacché, Yuliya Knyazhnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonethen Downar

Summary

Background Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) by use of high-frequency (10 Hz) left-side dorsolateral prefrontal cortex stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37–5 min for a standard 10 Hz treatment session. We aimed to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

Figure 1: Change in HRS-D-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups

Data are mean scores with lower and upper 95% CIs.

Patient Referral

• For patients with medication resistant depression

• Must be under care of psychiatrist

• Referral form on tmslab.org or call: 667-0307
Initial Evaluation

- Referral from treating psychiatrist
- Neurology
  - Contraindications
  - Effect of medication on TMS
- Psychiatry
  - Caution if: Psychotic depression, bipolar, personality disorders
  - At least one adequate trial of antidepressant medication
# BIDMC Treatment Protocols

<table>
<thead>
<tr>
<th>Site</th>
<th>Hemisphere</th>
<th>Frequency</th>
<th>Duration</th>
<th>Wait time</th>
<th>Repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC (5.5 cm)</td>
<td>Left DLPFC (110% MT)</td>
<td>20 Hz</td>
<td>2 seconds</td>
<td>28 seconds</td>
<td>40 (1600 pulses)</td>
</tr>
<tr>
<td>Neuronetics</td>
<td>Left DLPFC (120% MT)</td>
<td>10 Hz</td>
<td>4 seconds</td>
<td>26 seconds</td>
<td>75 (3000 pulses)</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Right (110% MT)</td>
<td>1 Hz</td>
<td>1600 seconds</td>
<td>N/A</td>
<td>1 (1600 pulses)</td>
</tr>
<tr>
<td>Brainsway</td>
<td>Left DLPFC (120% MT)</td>
<td>18 Hz</td>
<td>2 seconds</td>
<td>20 seconds</td>
<td>55 (1980 pulses)</td>
</tr>
</tbody>
</table>
Consent

• Discussion of on-label vs. off-label treatment

• Explanation of side-effects
  – Seizure
  – Headache
  – Neck pain
  – Scalp pain
Initiation Phase

- Treatments daily (excluding weekends)
- Various mood assessments daily/weekly/monthly
- Minimum 2 weeks
- Maximum 4-6 weeks
Assessment tools

- Beck, Hamilton, Analogue scale
- Target symptoms
- Clinician evaluation of patient
- Other sources of information (e.g. family, referring psychiatrist)
- Side effects questionnaire
- Weekly meeting of all staff to discuss progress
Maintenance Phase

• Minimal evidence (absence of evidence, not evidence of absence)

• Relapse prevention
  – Start with weekly treatment
  – Gradually space out sessions

• “Watchful Waiting”
  – Patient presents when feeling worse
Alternatives being investigated

• Choosing protocol/frequency based on clinical parameters (anxiety, risk of mania/sz)
• Using rs-fMRI guidance for targeting
• Using anatomical MRI to help with intensity of stimulation (particularly in elderly)
• Plasticity measures as guide
• Multiple Sessions per day?
Conclusions

• TMS can be used to affect brain circuitry
• TMS has potential therapeutic effects for certain neuropsychiatric disorders
• It is FDA cleared for treatment of medication resistant depression
• The future is very bright, but rigorous investigation is required
Cost

• Insurance coverage depends on location
  – Medicare jurisdiction
  – Private payers
• Additional fee for assessments
• Helping with billing, talking with payers
rTMS in the clinical practice - Should we include this therapy in the depression decision tree? And where?

Based on the American Psychiatric Association guideline for depression treatment
I am confident that I know how to refer patients for rTMS

- Mean 2.71 (3.5 is neutral)
- Disagree 69.9%, Agree 30.1%
I will likely refer patients for TMS in the future

- Mean 3.76
- Disagree 31.6%, Agree 68.4% (even though they don’t know how!)
I am confident that TMS is covered by most insurance plans

- Mean 2.30
- Residents 2.05, Faculty 2.52 (p<0.01)
- Academic 2.20, Community 2.59 (p=0.092) approaches significance
I feel that TMS is an effective treatment for treatment-resistant depression:

- Mean 3.82
I know and understand the FDA indications for TMS use in treatment-resistant depression:

- Mean 2.89