Disclosures

Todd Hutton, M.D.
- Speaker for Neuronetics
- Board of Directors, Clinical TMS Society

Richard Bermudes, M.D.
- President, Clinical TMS Society
- Private Practice, TMS Health Solutions, PC

Kimberly Cress, M.D.
- Board of Directors, Clinical TMS Society
How TMS Works

TODD HUTTON, M.D.
Faraday’s Law: A time-varying magnetic field induces an electric current that runs perpendicular to the time varying motion of the magnetic field.
The First TMS Device

Tony Barker, Ph.D. and the Sheffield group with the stimulator which first achieved TMS, February 1985.

From left to right: Reza Jalilous, Ian Freeston and Tony Barker
What if you could stimulate the brain hundreds or thousands of times?

Why would you want to do that?

Mark George, M.D.
MUSC
The Depressed Brain

![Brain scans comparing depressed and not depressed states.](image-url)
Brain Stimulation: What’s Old is New Again

Electroconvulsive Therapy (ECT) is still our most effective depression treatment, and yet one of the least commonly used.

Other forms of Neuromodulation or Brain Stimulation include:

• Convulsive therapies: ECT and Magnetic Seizure Therapy (MST)
• Sub-Convulsive but still firing neurons: Vagal Nerve Stimulation (VNS) and Transcranial Magnetic Stimulation (TMS)
• Sub-Convulsive and not firing neurons: Transcranial Direct Current Stimulation (tDCS)
Energy Delivery to the Brain

• 2000-5000 pulses per day
• 20-60 minutes, awake, unmedicated
• 5 days per week (Eloise’s Rule)
• 6 weeks (also a convention)

Leads to...
Brain Effects

• Release of BDNF (Brain Derived Neurotrophic Growth Factor)
• Neuronal growth as seen in animal studies
• Long Term Potentiation in neurons
• Changes throughout the network and not just local to the magnet pulse
Effects of a Single Pulse

Sustained Effects of Treatment
Before and After Subtraction SPECT Study

Transcranial Magnetic Stimulation: The Four Magnets

KARL LANOCHA, M.D.
Basic Parts of TMS Device

Diagram showing the basic parts of a TMS device:
- Power Supply
- Capacitor
- Switch
- Coil
  - Electric current
  - Magnetic field
  - Electric field
Electrical Diagram
NeuroStar, Magstim, Magventure

Figure 8 Coil

**Focused** Magnetic Field
Penetration: 2.4 cm
Brainsway

H Shaped Coil

**Diffuse** Magnetic Field
Penetration: 2.6 cm
**Coil Design**

- **H1 Coil**
  - Brainsway
  - Coil Design
  - Electric Field (V/cm)
  - Depth: 2.6
  - Stimulated Brain Volume (%): 4.6

- **Figure 8 Coil**
  - Neuronetics, Magstim, Magventure
  - Coil Design
  - Electric Field (V/cm)
  - Depth: 2.4
  - Stimulated Brain Volume (%): 0.6

**H1 Coil is 8.3% deeper and 667% less focal than Figure 8 coil**
Other Considerations

• Efficacy and safety
• Off label use
• Provider experience
• Patient experience
• Cost to provider
• Cost to patient
Efficacy and Safety

Efficacy

- Figure 8 metanalyses: 18.6% remission
- H1 (industry sponsored): 32.6% remission
- No head to head comparison
- Possible increased seizure risk with H1 coil
Off Label Use

• Figure 8 coil easy to reposition
• H1 helmet limits targeting ability
  • New helmet designs may allow treatment of other conditions
• Theta burst
Provider Experience

- Customer support
  - Service
  - Reimbursement assistance
- Ease of use
- Graphic user interface
- EHR
- Portability
Patient Experience

- Comfort
- Time in chair
- Ability to converse
Cost

• Cost to provider
  • Purchase vs. lease
  • Disposable costs
• Cost to patient
  • No clear differences
Summary

• All TMS devices function in a similar manner
• Important differences in design, cost, and ease of use
• Try as many different devices as you can
• Consider using more than one device in your practice
Clinical Efficacy and Safety of TMS for Depression

RICHARD BERMUDES, M.D.
Large-Scale Randomized Controlled Trials (RCT’s)

- Four large-scale studies (sample size > 100)
- Two large multicenter industry supported trials that lead to FDA approval for two devices
- One NIH-funded study with dosage parameters similar to those in the industry-sponsored study but with sham design enhancements
- One European study of the augmentation effects of TMS when used in combination with pharmacotherapy

George et al., Archives of General Psychiatry. 2010(67);507-516
Herwig et al., British Journal Psychiatry. 2007;191, 441-448
Levkovitz et al., World Psychiatry. 2015(14); 64-73
O’Reardon et al., Biological Psychiatry. 2008(62); 1208-1216
NIH-Sponsored OPT-TMS Trial

• Four University Clinics
• 199 antidepressant-free patients with mean lifetime failure of 3.3 ADM
• TMS to LDLPFC for 3 weeks (15 sessions)
• Odds of attaining remission was 4.2 times greater with active vs. sham

George et al., Archives of General Psychiatry. 2010(67); 507-516
Summary of TMS Acute Unipolar Depression Trials

• Four Large Prospective RCT’s support TMS for treating acute to moderately treatment-resistant depression
• Remission rates from 15%-30% in the double-blind phase, and 30% or more in open-label
• Safe and Tolerable
Meta-Analyses of TMS Efficacy in MDD

• At least 12 meta-analyses have been published with most of them finding that TMS is statistically superior to sham for the treatment of major depression

• McNamara et al. (2001) included five studies and reported a NNT of 2.3

• Holtzheimer et al. (2001) included 12 studies in their analysis and obtained an effect size of 0.81

• Slotema et al. (2010) pooled data from 34 RCT’s with a total sample of 1383 patients and obtained an effect size of 0.55
Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis

- Evaluate the efficacy of TMS in patients with treatment-resistant depression (TRD)
- Included 18 TRD studies published from Jan 1980 – March 2013
- Those receiving TMS were 3 times more likely to respond and 5 times more likely to obtain remission vs. those who received sham
No Efficacy Effectiveness Gap

Carpenter Study
- Open Label
- 307 Real World Patients
- Medications and other treatments allowed

Connolly Study
- Open Label
- 100 Real World Patients
- Medications and other treatments allowed


## Private Practice Outcomes

### Patient Characteristics for Acute Course of Transcranial Magnetic Stimulation (n = 74)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>50 (14.0)</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>23 (31%)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (69%)</td>
</tr>
<tr>
<td>MDD, n (%)</td>
<td>66 (89%)</td>
</tr>
<tr>
<td>Bipolar Disorder, n (%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Duration of current MDE</td>
<td></td>
</tr>
<tr>
<td>&gt;1y, n (%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>1-2y, n (%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>&gt;2y, n (%)</td>
<td>55 (74%)</td>
</tr>
<tr>
<td>History of ECT, n (%)</td>
<td>7 (9%)</td>
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<tr>
<td>History of prior hospitalization, n (%)</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>Number of ADM attempts</td>
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</tr>
<tr>
<td>0, n (%)</td>
<td>0 (0%)</td>
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<tr>
<td>1, n (%)</td>
<td>2 (3%)</td>
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<td>2, n (%)</td>
<td>3 (4%)</td>
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<tr>
<td>3, n (%)</td>
<td>5 (7%)</td>
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<tr>
<td>≥4, n (%)</td>
<td>64 (86%)</td>
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</table>

Abbreviations: ADM = antidepressant medication, ECT = electroconvulsive therapy, MDD = major depressive Disorder, MDE = major depressive episode

### PHQ-9 Response and Remission Rates

- **Response Rate - 50% Improvement from consult score**
- **Remission - after taper score of 4 or below**
- **Mild - after taper score of 9 or below**
TMS: Contraindications

Non-removable metallic objects in or around the head

• Conductive, ferromagnetic or other magnetic sensitive metals that are implanted or are non-removable within 30 cm of treatment coil
• Implanted electrodes/ stimulators
• Deep Brain Stimulator
• Aneurysm clips or coils
• Cochlear implants
• Stents
• Bullet or other metal fragments
Time Course for Most Common Adverse Events

Time Course of Incidence of Headache in RCT

Time Course of Incidence of Application-Site Pain in RCT

Active TMS (n=155)

Sham TMS (n=146)

Potential Serious Adverse Events

• Cognition
• Suicide Ideation
• Seizures
TMS and Cognition

BSRT Short Term Recall

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<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 6</th>
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<tbody>
<tr>
<td>40</td>
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<td></td>
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<tr>
<td>50</td>
<td></td>
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<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
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BSRT Delayed Recall

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<th>Week 4</th>
<th>Week 6</th>
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<tr>
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</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
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Mini Mental Status Exam Scores

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<th>Week 4</th>
<th>Week 6</th>
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<tbody>
<tr>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
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AMI-SF Amnesia Scores (%)

<table>
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<th></th>
<th>Week 4</th>
<th>Week 6</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>50</td>
<td></td>
<td></td>
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<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
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</table>

Emergence of Suicidal Ideation: Multicenter Study

* 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.

TMS and Seizures

• Seizure is the most serious side effect associated with TMS
• Most cases associated with TMS were prior to the publication of the TMS safety guidelines in 1998
• Considering the large number of healthy individuals and patients who have undergone TMS sessions since 1998 and the small number of seizures reported, the risk of TMS to induce seizures could be considered very low.

TMS Maintenance and Durability

KIMBERLY CRESS, M.D.
Multisite Naturalistic Observational Study of TMS for MDD: Acute Treatment Outcomes and One-Year Follow-Up

Study Goal: Define real world outcomes associated with TMS Therapy across a broad spectrum of patients and practitioners

42 Sites: Comprised of institutions and private practice

307 Patients: Unipolar, non-psychotic MDD patients in acute phase

Acute Phase
Treatment course driven by patient clinical response

Long-term Outcomes
Measured at 3, 6, 9 and 12 months

Patients Who Entered Study Had Significant Morbidity

<table>
<thead>
<tr>
<th>Patient and Treatment Characteristics</th>
<th>N = 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) Female</td>
<td>205 (66.8)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>48.6 (14.2)</td>
</tr>
<tr>
<td>Disease and Treatment History N(%)</td>
<td></td>
</tr>
<tr>
<td>- Recurrent Major Depression</td>
<td>285 (92.8)</td>
</tr>
<tr>
<td>- Comorbid Anxiety Disorder</td>
<td>46 (15.0)</td>
</tr>
<tr>
<td>Psychiatric Treatment History N(%)</td>
<td></td>
</tr>
<tr>
<td>- History of Inpatient Hospitalization</td>
<td>133 (43.3)</td>
</tr>
<tr>
<td>- History of ECT Treatment</td>
<td>15 (4.9)</td>
</tr>
<tr>
<td>Prior Antidepressant Medication Treatment mean (SD)</td>
<td></td>
</tr>
<tr>
<td>- Average Number of Adequate Treatments in Current Episode</td>
<td>2.5 (2.3)</td>
</tr>
<tr>
<td>Mean (SD) Number of TMS Sessions During Acute Treatment</td>
<td>28 (10.1)</td>
</tr>
</tbody>
</table>

Carpenter, Depression and Anxiety, 2012
Comparison of End of Acute Treatment Clinical Status: Clinician-and Patient-Assessed Outcomes

**Clinician Rating**
*CGI-Severity of Illness*

- Markedly ill or worse
- Moderately ill
- Mildly ill or better

**Patient Rating**
*PHQ-9 Scale*

- Markedly ill or worse
- Moderately ill
- Mildly ill or better

LOCF Analysis of intent-to-treat population

Remission is Possible with TMS Therapy: 1 in 2 Patients Respond, 1 in 3 Achieve Remission

Carpenter (2012), Depression and Anxiety
Long-Term Phase Results at 12 Months

Outcomes measured for one year following end of acute treatment

- Physician directed standard of care
- 36.2% of patients received TMS reintroduction
- Average number of TMS treatment days = 16

Long term durability of effect has not been established in a controlled trial

“It is notable that TMS reintroduction was successful in rescuing most patients with threshold deterioration and returning them to their prior level of depressive symptom relief.”

Important observation given:

- The chronic and relapsing nature of pharmacoresistant major depression
- Absence of definitive data suggesting that re-treatment with previously effective medications is capable of doing the same.

The results provide support for long-term treatment strategy that incorporates retreatment with TMS for patients who showed positive response to an initial acute course. (p.257)
Patient Selection and Insurance
Who is Right for TMS Therapy?

Indicated for:

• TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medications at or above the minimal effective dose and duration in the current episode

Patient Characteristics:

• In a recurrent episode
• Multiple medication attempts, yet still symptomatic
• Considering a complex drug regimen
• Experience frequent side effects from medication

Carpenter, et al. (2012), Depression and Anxiety
After 6 weeks of acute phase treatment, NeuroStar TMS Therapy achieved statistically significantly superior outcomes as measured by QIDS-SR total scores compared to next choice antidepressant medication treatment. When compared to a propensity score matched sample of patients in the STAR*D Study.
TMS Therapy: A Well-Tolerated Antidepressant (Adverse Events with Incidence >5% and 2x control)

**TMS Side Effects**
- Scalp Pain or Discomfort at Treatment Site

**Systemic Drug Side Effects**

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Nervousness</th>
<th>Weakness</th>
<th>Abnormal Ejaculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Anxiety</td>
<td>Dry Mouth</td>
<td>Impotence</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Increased Appetite</td>
<td>Dizziness</td>
<td>Sweating</td>
</tr>
<tr>
<td>Nausea</td>
<td>Decreased Appetite</td>
<td>Fatigue</td>
<td>Tremor</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Decreased Sexual Interest</td>
<td>Headache/Migraine</td>
<td>Treatment Discontinuation Side Effects</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TMS is Included in Practice Guidelines Following Failure of Initial Treatment

American Psychiatric Association (2010)

“...Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy...”

World Federation of Societies for Biological Psychiatry (2009)

Canadian Network for Mood and Anxiety Treatments (2009)

Institute for Clinical Systems Improvement (2010)
TMS Insurance Coverage

- TMS has coverage in every state for Major Depressive Disorder
- Covered by all major private insurance companies, except Aetna
- Covered by Medicare in every state
- Coverage policies vary, but most typically require a failure of 3-6 antidepressant medications from different classes and Psychotherapy

248.4 M Covered Lives
Conclusion

• TMS is focal non-invasive form of brain stimulation based on principles of electromagnetic induction that has been well established for nearly 200 years.

• TMS is a safe and effective treatment of moderate to severe MDD

• TMS is well-tolerated and without risks of systemic side effects seen with medications

• TMS needs to be considered as treatment option
Thank You For Your Time

Q&A