Transcranial Magnetic Stimulation (TMS) Therapy

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Major Depressive Disorder

Treatments of MDD

- Pharmaceuticals
- Psychotherapy
- Neuromodulation
- Other therapies
Neuromodulation

- Transcranial Magnetic Stimulation
- Vagal Nerve Stimulation
- Deep Brain Stimulation
- Electroconvulsive Therapy
Transcranial Magnetic Stimulation
What is it?

• Application of electromagnetic induction described by Michael Faraday in 1839

  • Faraday’s Law: a time-varying magnetic field induces an electric current that runs perpendicular to the time-varying motion of the magnetic field\(^1,2\)

• Clinical application: Pulsed magnetic fields can induce electrical currents in brain tissues and neurons\(^3\)

Transcranial Magnetic Stimulation
What is it?

**LTP**
- High frequency trains (a series of stimuli) delivered to a presynaptic neuron will result in substantial post-synaptic response over an extended period of time
- Learning?

**LTD**
- Opposite LTP
- Reduction of receptor density
Transcranial Magnetic Stimulation

- High Frequency = Greater than 5HZ is excitatory
- Low Frequency = Less than or equal to 1HZ is inhibitory
Major Depressive Disorder

In MDD, some areas of the brain are hypoactive and others are hyperactive.
When there is an appropriate amount of monoamine neurotransmitter activity, neuronal activity throughout the brain functions normally.

- Monoamine dysfunction is linked to MDD
- Malfunctioning circuits lead to specific symptoms

Regions implicated in MDD are connected to the brainstem via monoaminergic circuits. monoamine neurotransmitter projections

- Concentration
- Pleasure/interests
- Psychomotor fatigue (mental)
- Guilt
- Suicidality
- Worthlessness
- Mood
- Sleep
- Appetite
- Psychomotor fatigue (physical)
- Pleasure/interests

Major Depressive Disorder: Circuits and Neurotransmitters

- Serotonin (5-HT)
- Dopamine (DA)
- Norepinephrine (NE)
NeuroStar Releases Neurotransmitters in the Brain

Depolarization of neurons in the DLPFC causes local neurotransmitter release

Depolarization of pyramidal neurons in the DLPFC causes neurotransmitter release in deeper brain neurons

Activation of deeper brain neurons then exerts secondary effects on remaining portions of targeted mood circuits

These effects are associated with improvements in depressive symptoms


Dorsolateral prefrontal cortex

Cingulate cortex
Chemical Antidepressants

Therapeutic Effects such as:
- improved mood
- reduced feelings of guilt, suicidality, and worthlessness
- increased concentration
- agitation

Side Effects such as:
- blurred vision
- dry mouth
- nausea
- GI distress
- sexual dysfunction
- weight gain
- insomnia
- fatigue
- blood pressure changes
- weight gain

Chemical Antidepressants

Antidepressant
Key TMS 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
Transcranial Magnetic Stimulation

- Left sided HF-TMS: Antidepressant
- Left sided LF-TMS: Possible AD Effect
  - Right sided HF-TMS: ?
  - Right sided LF-TMS: Anxiety
- Right sided HFTMS + R LF-TMS
Motor Threshold (MT)

- **Location**: position on motor cortex that stimulates thumb
- **Level**: minimum stimulation that induces observable motor response in 50% of applied pulses
- **% MT**: pulse output used for treatment, relative to MT level
FDA Approved Device TMS Therapy: Treatment Parameters

- Treatment sessions
  - 37.5 minutes
- Treatment course
  - 5x/week for 4 to 6 weeks
  - Then taper over 3 weeks
- Treatment magnetic field strength = 120% of motor threshold
- Treatment parameters
  - Stimulation time = 4 seconds
  - Pulses per second = 10
  - Interval = 26 seconds
  - Number of pulses = 3000

FDA Approved Device TMS Therapy: Study Population

Inclusion criteria:
- DSM-IV diagnosis of unipolar MDD
- Current episode \( \leq 3 \) years
- 1-4 dose and duration adequate treatment failures
- No current medication for MDD

Exclusion criteria:
- History of psychosis, bipolar disorder (BPD), obsessive-compulsive disorder (OCD)
- Posttraumatic stress disorder (PTSD) or eating disorder \( \leq 1 \) year
- Neurological contraindication

1:1 randomization
301 evaluable patients

FDA Approved Device TMS Therapy: Overall Efficacy in RCT

MADRS Total Score (Baseline to Endpoint Change)

Baseline Week 2 Week 4 Week 6

Change From Baseline

P = .191
P = .057
P = .058

HAMD-24 Total Score (Baseline to Endpoint Change)

Baseline Week 2 Week 4 Week 6

Change From Baseline

P = .051
P = .012
P = .015

* $P < .05.$
LOCF, LS mean.

## FDA Approved Device TMS Therapy: Indicated Patient Population

<table>
<thead>
<tr>
<th>Treatment history (current episode)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Median number of antidepressant treatments attempted (range)</td>
<td>4 (1–23)</td>
</tr>
<tr>
<td>• Number of antidepressant treatments at adequate dose and duration</td>
<td>1</td>
</tr>
</tbody>
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TMS Therapy Produced Significant Improvements in Depressive Symptoms (FDA Indicated Population)

**P** = .007

**P** = .0006

**P** = .0041

MADRS Total Score (Baseline to Endpoint Change)

**P** < .01.

LOCF analysis of evaluable study population.


NeuroStar TMS Therapy (n=88)

Sham (n=76)
TMS Therapy: Significant Improvement of HAMD Factor Scores
(FDA Indicated Population)

Core Depression

Anxiety/Somatization

Psychomotor Retardation

Change From Baseline*

Baseline Wk 2 Wk 4 Wk 6

Baseline Wk 2 Wk 4 Wk 6

Baseline Wk 2 Wk 4 Wk 6

* P<.05; ** P<.01.
LS Mean; LOCF.

OPT TMS Trial

Prospective, multisite, randomized, active sham-controlled (1:1 randomization), duration-adaptive design with 3 weeks of daily weekday treatment (fixed-dose phase) followed by continued blinded treatment for up to another 3 weeks in improvers.

199 Subjects

p = 0.02
6-Month Long-Term Follow-up Study: Results

- Patients previously treated with TMS Therapy had an 14% relapse rate at the end of 6 months
- ~38% experienced symptom breakthrough and required TMS Therapy retreatment
- ~85% responded to reintroduction of TMS

Treatment Utilization and Outcomes Study Protocol No. 19-50001-000

• Goals
  • Define real world outcomes associated with NeuroStar TMS Therapy across a broad spectrum of patients and practitioners
  • Examine one year patient outcomes

• Patient Population & Sites
  • 309 evaluable unipolar, non-psychotic MDD patients in acute phase
  • 41 sites comprised of institutions and private practice

• Study Duration
  • 2 years for entire study
  • Per patient: 6 weeks (full acute); 12 month follow-up

• Patient Treatment
  • Clinical care as usual with 6 clinical assessments at 7 time points
TMS Shows Significant Improvement in Both Clinician and Patient Assessed Outcomes (N=99)

Before Treatment           After Treatment

**Patient-Reported Outcomes**

- **Neuronetics, Inc. (data on file)** - Interim Study Analysis

**Clinician-Reported Outcomes**

- **CGI-Severity Rating 1 or 2 (Mild or No Depression)**
  - Before Treatment: 0%
  - After Treatment: 45.4%

- **PHQ-9 Total Score <10 (Mild or No Symptoms)**
  - Before Treatment: 6.1%
  - After Treatment: 67.4%
Clinically Meaningful Response and Remission Rates in Real World Clinical Practice (IDS-SR, Patient-Reported) (N=99)

1 in 2 patients respond and 1 in 3 patients achieve remission

Neuronetics, Inc. (data on file) – Interim Analysis

LOCF Analysis of intent-to-treat population
Response: >50% reduction in score, Remission: final score < 15
Other Uses

- PTSD: Right sided HF-DLPFC
- Bipolar Disorder
  - Depression RCT = zero benefit  Open Label = modest benefit
  - Mixed: Possible LF DLPFC
  - Mania: HF (20HZ) RDLPFC
- Dementia: HF Bilateral DLPFC or LF Bilateral DLPFC
  - Modest benefit
- Schizophrenia: Left sided HF-DLPFC
  - Moderate effect size
Other Uses

• OCD: No favorable results yet
• ADHD: No real data
• ASD: High functioning Autism and Aspergers patients had positive results in social relating impairments
  • HF Bilateral Dorsomedial prefrontal cortex
TMS Therapy: Safety Overview

- No systemic side effects
- No adverse effect on cognition
- Most common adverse event associated with treatment was scalp pain or discomfort
  - < 5% of patients discontinued due to adverse events
- No seizures with NeuroStar device during clinical studies
  - (over 10,000 treatments)
- Rare risk of seizure with NeuroStar TMS in post-market use
  - (0.003% per treatment, <0.1% per acute treatment course)
  - (>200,000 treatments in post-marketing experience to date)
- Long term safety demonstrated in 6 months follow-up

Contraindications

• Aneurysm clips or coils
• Carotid or cerebral stents
• DBS Electrodes
• Metallic devices implanted in the head
• Magnetically active dental implants
• Cochlear/otologic implants
• CSF shunts
• Ferromagnetic ocular implants
• Pellets, bullets, fragments less than 30 cm from the coil
• Facial tattoos with metallic ink, permanent makeup less than 30 cm from the coil
Remove Before Treating

• Wearable physiologic monitors (e.g. Holter)
• Bone growth stimulators
• Portable glucose monitors
• Hearing aids
• Cell phones/PDA’s
• Removable dentures/bridgework (Risk: Device may become disabled or overheat resulting in heat related injury).
Conclusions

• FDA Cleared for MDD
• APA Treatment Guidelines support TMS
• No systemic side effects
• No anesthesia or cognitive deficits