TREATING DEPRESSION WITH TRANSCRANIAL MAGNETIC STIMULATION

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DISCLOSURES

- Past speaker: Bristol Myers Squibb
- Past speaker: Neuronetics
- Past investigator: Neuronetics
- What is TMS?
- Recent research on TMS
- Clinical experience with TMS
- Summary
GEORGE MS, BELMAKER RH. TRANSCRANIAL MAGNETIC STIMULATION IN CLINICAL PSYCHIATRY. ARLINGTON, VA: AMERICAN PSYCHIATRY PUBLISHING INC.; 2007.
NEUROSCIENCE HAS EVOLVED LOCALIZATION OF FUNCTIONING/BEHAVIOR

- Trepanning
- Phrenology
- SPECT/PET/MRI
- TMS is a tool to advance understanding
- TMS depends on magnetic fields converted into electrical energy
- Electromagnetic energy
- Discovered in 1831 by Faraday
1902- Beer and Pollacsek filed for a patent using an electromagnetic coil placed over the skull to treat “depression and neurosis”

1910- phosphene production by magnetic field

1959- magnetic field stimulates peripheral frog muscle

TMS Circuit

- Power supply
- Bank of capacitors
- TMS coil
MECHANISM OF ACTION

- Creation of Transmembrane Potential-action potential along axon membrane

- Spatial Derivative-change of electrical field along neuron
○ Single pulse used for cortical mapping and electrophysiological studies

○ r(repetitive)TMS delivers trains of stimuli up to 60 hertz with a biphasic pulse of 200-300 microseconds
TMS in Depression

- Focal stimulation

- Mood circuits include cortico-cortical and cortico-subcortical-motor cortex connections of the dorsolateral prefrontal cortex with the limbic system
STIMULATION PARAMETERS IN CLINICAL TRIALS 1993-2006 (40 STUDIES)

- MT range = 0.3-120%
- Hertz range = 0.3-20
- # Sessions 1-30
- Total pulses 30-26,000
Body of literature is growing
Earlier studies may be considered inadequate due to inadequate dosages and durations of TMS
Small sample sizes
Research directions include larger sample sizes, multicenter collaboration, maintenance strategies, parallel designs with stimulation variables
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

Major Depressive Disorder: Circuits and Neurotransmitters

Regions implicated in MDD are connected to the brainstem via monoaminergic circuits

Monoamine Neurotransmitters

- Serotonin (5-HT)
- Dopamine (DA)
- Norepinephrine (NE)
DIRECTLY DEPOLARIZES CORTICAL NEURONS

Depolarization leads to action potentials in local neurons and thereby releases neurotransmitters.

Pulsed magnetic fields:
- induce a local electric current in the cortex which depolarizes neurons
- elicit action potentials
- cause the release of chemical neurotransmitters

Neurons are “electrochemical cells” and respond to either electrical or chemical stimulation.
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.
TMS AND DEPRESSION

- 14 million US adults with depression annually

- The World Health Organization indicates unipolar major depression will be the most significant cause of disability worldwide in 2030.

Reference provided by Richard Shelton, MD at UAB

There is a 40% increase in medical costs for patients with treatment resistant depression
WWW.CLINICALTRIALS.GOV

- TMS = 537 studies
- TMS Depression = 157 studies
Smoking Cessation
Depersonalization Disorder
Bipolar Depression
Tourette’s Syndrome
Alzheimer’s Disease
Schizophrenia
Suicidal Ideation
Migraine
Mild Cognitive Impairment
Pain
PTSD
OCD
RESEARCH OVER THE PAST FIVE YEARS
Treatment of 85 patients who received sham TMS in previous 6 week study and 73 patients who did not respond to 6 weeks of TMS in the preceding RCT.

Diagnosis of Major Depressive Disorder

Left prefrontal TMS, 5 x week, 10 hertz, 120% MT, 3000 pulses per session

Outcome measure was change in MADRS. Response was 50% reduction. Remission was score less than 10.
Sham TMS:

response = 42.4%,
remission = 20.0%

Previous non response:
response: 26.0%
remission: 11.0%
2-arm, double-blind, randomized, controlled trial
60 patients with TRD
Right 1-HZ rTMS in continuous 15 minute train
Priming stimulation of either twenty 5-second, 6-Hz trains or an equivalent sham preceded the 1-Hz stimulation.
Primary outcome variable was reduction in MADRS
Response: active-priming = 33%,
sham-priming = 14%
55 patients failed to respond to 1 or 2 Hz right DLPFC rTMS, 100 % MT, 10 Hz x 5 sec or 5 Hz x 10 sec x 20 sessions 1500 pulses daily x 10 sessions Outcome: 50% reduction in MADRS 10 Hz = 27.2% response 5 Hz = 24.1% response
- 301 patients with Major Depression in multisite, sham-controlled trial with open-label extension

- Left DLPFC, 10 Hz, 120% MT, 3000 pulses q day, 20-30 sessions
RANDOMIZED CONTROLLED TRIAL POSITIVE PREDICTORS

- Current illness less than 2 years
- One adequate treatment this episode
OPEN-LABEL EXTENSION TRIAL POSITIVE PREDICTORS

- Female
- Single episode of illness
- Lower baseline motor threshold
20 patients with TRD

- Five 60-s 1-Hz trains right DLPFT x twelve treatments
- Responders defined as greater/equal 50% decrease in HDRS
- TSH, fT3 and fT4 were measured
- No significant changes in fT3 and fT4
- TSH levels of responders were lower pre-TMS
- TSH levels of responders rose and levels of non-responders declined
- 74 patients with MDD treated with adequate antidepressant dose for 4 weeks
- Randomized to HFL or LFR rTMS
- HFL = 15 Hz, 20 trains of 30 pulses, 600 pulses/day x 10
- LFR = 1 Hz, 2 trains of 300 pulses, 600 pulses/day x 10
- HFL responders = 65.6%
- LFR responders = 57.1%
- Activity level was a negative predictor of response in both groups
- Baseline anxiety was a negative predictor for the HFL group
14 depressed patients not responding to at least one antidepressant

15 rTMS sessions over 2 days

5 consecutive hourly sessions on Day 1 and 10 consecutive hourly sessions on Day 2

10 Hz rTMS, 5 second trains, 25 sec intertrain interval, 100% MT

Each hourly session included 20 rTMS trains over 10 minutes

15,000 rTMS pulses over two days
**Mean HDRS24 Decrease**

- Day 3 = 47%
- Week 3 = 45%
- Week 6 = 55%
RESPONSE

- Day 3 = 43%
- Week 3 = 36%
- Week 6 = 36%
REMISSION

- Day 3 = 29%
- Week 3 = 36%
- Week 6 = 29%
Gender, age, age of onset, duration of current episode, number of lifetime episodes, and number of treatment failures in the current episode were not associated with percent change.
- NIMH study at four U.S. university hospital
- 199 patients with MDD
- Insufficient clinical benefit to 1-4 adequate medication trials or intolerant to 3+ trials
- Randomized, active sham-controlled with 3 weeks of active treatment followed by continued double blind treatment for up to another 3 weeks
- rTMS, 120% MT, LDLPFC, 10 Hz, 3000 pulses/session, 3 weeks + 3 weeks
- 88% retention rate
- Outcome = MADRS
- 3 week remission rate = 9.5%
- 6 week remission rate = 29.9%
301 patients randomly assigned to active or sham TMS in a 6-week controlled trial

120% MT, 10 Hz, 3000 pulses/session

Non-responders could enroll in a second, 6-week, open trial

Patients with partial response (greater than 25% decrease in HAMD) were tapered off TMS over 3 weeks and monitored over 24 weeks on maintenance antidepressant monotherapy

TMS was administered again if criteria for symptom worsening was met
Relapse was primary outcome measure
Secondary outcome measures included change from baseline in MADRS/HAMD
47.2% reached partial response at 3 weeks
40% responded after additional 3 week taper
99 patients entered 24 week follow-up
10% met criteria for relapse
84.2% achieved mood stability again with TMS
9 antidepressant-free women with postpartum depression
20 rTMS over 4 weeks, 10 HZ, 120% MT, LDLPFC
Primary outcome variable was reduction in HRSD-24 (remission < 10)
8 remitted at 4 weeks
7 remained in remission at 6 months w/o medications, 1 was lost to f/u
59 year old man with four recurrences of depression responded “dramatically” to TMS

- LFRS (1 Hz, 100% MT, 4320 total pulses)
- HFLS (10 Hz, 100% MT, 12,000 total pulses)
- Twelve sessions during three weeks
- HDRS 24 at baseline, 5 at week four, 2 at month 6
- Areas of hypoperfusion in the anterior and subgenual cingulate cortices were almost unchanged at week 4 but were normalized at month 6
15 patients with treatment-resistant MDD
Continued antidepressants
Left DLPFC, 10 Hz, 120%, 3000 pulses per session x 4 weeks, 20 sessions, 60,000 pulses
Mean decrease in IDS-SR = 20.3%
Mean decrease in HAM-D24 = 15.4%
Statistically significant improvement in WHOQOL BREF (World Health Organization’s Quality of Life Measure-Brief Version)
Ten women with MDD in second or third trimester
- Right DLPFC, 20 sessions, 1 Hz, 100% MT, 6000 pulses
- Seven of ten responded with decrease of 50% or greater in HDRS-17
- Antenatal monitoring was performed at sessions 1, 10, and 20
- No adverse pregnancy or fetal outcomes observed
Retrospective cohort study examined 100 patients treated for depression, MDD (65) or BAD (20) between July, 2008 and March 2011.

HDRS equal/greater than 14 or BDI equal/greater than 16 (85 patients met criteria).

Existing psychotrophics continued.

TMS was left DLPFC, 10 Hz, 110 or 120% MT, 4000-8000 pulses/session +/- right DLPFC, 1 Hz, 300-1200 pulses/session x 30 sessions total.
Primary outcome = CGI-I with 50.6 % response rate and 24.7 remission rate

Secondary outcome= HDRS with 41.2% response rate and 35.3 % remission rate

For BAD Depression, CGI-I response rate was 35% and the remission rate was 15%
52 patients with Major Depression completed treatment
- Female 73.1%
- Male 26.9%
- Age range 21-84
- Average # treatments = 28
- 10 Hz
- 3,000-5,000 pulses per session
- MT range 0.7-1.49 at 120%
- Response rate = 88.5%
- Remission rate = 59.6%
SUMMARY
"...IT IS IMPORTANT TO NOTE THAT THIS DOES NOT CHANGE YOUR PSYCHOLOGY. IF YOU ARE DEPRESSED WITH AN UNSTABLE PERSONALITY, YOUR DEPRESSION MIGHT BE LIFTED BUT YOUR UNSTABLE PERSONALITY IS STILL THERE..."
Yip AG, Carpenter LL. Transcranial magnetic stimulation for medication-resistant depression. J Clin Psychiatry. 2010 Apr;71(4)
“rTMS is safe, well tolerated, and at least moderately efficacious for medication-resistant depression. However, questions remain about patient selection, how best to deliver the treatment (i.e., parameter optimization), and its place in the treatment algorithm relative to existing treatments for resistant depression.”
Husain MM, Lisanby SH. Repetitive Transcranial Magnetic Stimulation (rTMS), A Noninvasive Neuromodulation Probe and Intervention. Journal of ECT. 2011 Mar; 27(1)
“Neuromodulation represents an evolving science in the 21st century. Advances in this field will require further careful study of these techniques and will be facilitated by critical examination of the literature.”
GEORGE MS, POST RM. DAILY LEFT PREFRONTAL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR ACUTE TREATMENT OF MEDICATION-RESISTANT DEPRESSION. AM J PSYCHIATRY. 2011 APR;168(4):356-64
“The debate and research thus now shift from determining whether rTMS works in the acute setting to trying to improve the technology and maximizing its clinical effectiveness, utility, and durability.”
THANK YOU