Innovations in Neuromodulation:

Transcranial Magnetic Stimulation
DISCLOSURES

Michelle Cochran MD, DLFAPA, FCTMSS
NeuroScience & TMS Treatment Centers, PC; Chief Medical Officer, Partner & Shareholder
Cromwell Medical (MSO) Member
Nashville Center for Hope & Healing, Medical Director
Train Your Brain: Your Record of Care with TMS, co-author
Vanderbilt University Medical Center Department of Psychiatry, Clinical Faculty Member

Devices: Use NeuroStar & MagVenture devices in TMS practice; Shared Marketing w/ NeuroStar

Market research participant: Neuronetics & MagStim (2018)
Janssen Paid Speaker for Spravato: 2023
I have <$10,000 USD worth of Stock in a few TMS companies (Neuronetics, Brainsway)
SubPI in VNS study RECOVER by LivaNova; 2021 – present

American Psychiatric Association - ACROSS representative to APA; Appointed Chair of APA Caucus on Neuromodulation
Tennessee Psychiatric Association - current Vice President, former Secretary
Clinical TMS Society: Course Director for PULSES (honorarium, travel expenses); Non-voting Board member;
Education Committee member (past co-chair); Annual Committee member (past co-chair); Past Member of multiple
other committees: Legal, Business, & Ethics, Outreach, Research, Insurance; Former Voting Board member, Past
member of Exec Committee (2015-2019 as At-large member, VP-Elect, President, Past president)
• This continuing medical education activity includes device brand names for participant clarity purposes only. No product promotion or recommendation should be inferred.

• I, as a faculty member, I understand my responsibility to disclose to you, the audience, if I will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved – or cleared, as in the case of devices – by the US Food and Drug Administration).

• There was no TMS device industry involvement in the content of the slide deck.
• This slide deck was built from a slide deck which was originally conceived, produced, and edited by Clinical TMS Society Outreach Committee.

• The society’s board of directors approved the original slide decks for educating other clinicians in September 2017, since this time the slide deck has updated from the original 2017 version and has evolved into multiple slide decks and have been edited and updated by CTMSS Education Committee.

• This slide deck and subsequent versions have been used in conjunction with CTMSS by the American Psychiatric Association (APA); the Southern Psychiatric Association (SPA), US Psych Congress, multiple state psychiatric associations and many smaller regional and local state and community presentations.

• There are other FDA treatment clearances for repetitive TMS:
  • Obsessive Compulsive Disorder
  • Aid to Smoking Cessation
  • MDD with Anxious features
  • Single pulse TMS has been cleared for Migraine
Clinical TMS Society (CTMSS)

an international professional association of over 1000 physicians, clinicians, researchers, technicians, students, and industry partners dedicated to:

- Optimizing clinical practice of TMS treatment
- Increasing awareness of TMS therapy
- Improving accessibility of TMS therapy

www.clinicaltmssociety.org
Learning Objectives

• Review and describe the forms of electrical Neuromodulation used in Psychiatry

• Review the FDA-cleared indications, and clinically describe the research

• Review and consider whether TMS would be appropriate for a patient
Costs of Untreated Depression

- Depression is a common mental disorder
- Globally, more than 350 million people of all ages suffer
- Depression is the leading cause of disability worldwide and a major contributor to the global burden of disease
- Only 50% of individuals with depression seek help
- More than 30% do not receive adequate treatment from medication or psychotherapy

World Health Organization 2017
Depression, A *Brain Circuit Problem*

- Despite the predominance of pharmaceutical agents for treatment of depression, monoamine transmitters are only part of the depression picture; *the brain is an electro-chemical organ*

- Sophisticated forms of brain imaging are permitting scientists to understand the working brain and its circuitry

- These imaging technologies are leading towards understanding which brain circuits regulate mood and anxiety disorders
Major Depression is a Brain Disease

Mark S. George, MD. Fluorodeoxyglucose Positron Emission Tomography (PET) images acquired at the National Institute of Mental Health (NIMH), Bethesda, MD, 1994.
In depression, studies have found structural and functional dysfunction in frontal and prefrontal cortex, the anterior cingulate, and the limbic systems (amygdala, hippocampus, and the dorsomedial thalamus).
Neuromodulation Options for Depression

**Medications** (chemical neuromodulation)
SSRIs, SNRIs, TCAs, MAOIs, lithium, esketamine, other augmentation agents

**Psychotherapy** (behavioral neuromodulation)
CBT (Cognitive-Behavioral Therapy), DBT (Dialectical Behavioral Therapy), ACT (Acceptance and Commitment Therapy), Psychodynamic Therapy, Interpersonal Therapy, and Group Therapy

**Neurostimulation** (electrical neuromodulation)
ECT (Electroconvulsive Therapy), VNS (Vagus Nerve Stimulation), DBS (Deep Brain Stimulation), rTMS or TMS (repetitive Transcranial Magnetic Stimulation)
Chemical Neuromodulation
Antidepressant Medications

• When used first-line, antidepressant medications help patients reach remission about one-third of the time\(^1,^2\)

• A 2018 meta-analysis revealed that antidepressants had only a small to modest effect size of approximately 0.3\(^3\)

• With medication combinations and the development of pharmacogenomic testing we may, likely, improve outcomes

• Unfortunately, many patients still do not respond to medications or do not tolerate the side effects associated with the medications

STAR*D Revealed Reduced Likelihood of Remission with Each Treatment Trial

Medication Side Effects

- Increased or decreased sleep
- Changes in energy and fatigue
- Blurred vision
- Dry mouth
- Weight changes
- Appetite changes
- Sexual dysfunction
- Vital sign changes: blood pressure and pulse
- Gastrointestinal distress: nausea, vomiting, diarrhea, constipation

STAR*D: Discontinuing Treatment Increases with Each New Medication Attempt

Advantages of TMS Over TAU

• Unlike medications, TMS does not cause systemic side effects

• Unlike medications, which are prone to errors and non-adherence, TMS is an observed procedure during which proper administration is supervised

• TMS, like other neuromodulation, has proven to be effective in TRD for patients who have not responded to several medication trials

TMS vs Other Electrical Neuromodulation (ECT & VNS)

- FDA cleared for earlier in course of care, although some patients who fail ECT, respond to TMS and vice versa
- Non-invasive
- Office-based procedure that requires no sedation, anesthesia, hospitalization, or recovery time
- No known cognitive side effects with TMS

- ECT is ideal for MDD with psychotic features, acute hospitalized patients with suicidality, or catatonia
- ECT and VNS are ideal for highly refractory patients who have failed TMS and other outpatient treatments
Transcranial Magnetic Stimulation

History and Mechanism of Action
Science of TMS: 1831 Michael Faraday

- Physical principles of electromagnetism were discovered in 1831 by Michael Faraday; he observed that a pulse of electric current passing through wire coil generates a magnetic field.

- Rate of change (flux) of magnetic field determines the induction of a secondary current in a nearby conductor placed in a perpendicular plane.
TMS Physics, Using Faraday’s Law

- Time varying electrical current flows from Stimulator
- Time varying (pulsed) magnetic field emits from the TMS coil
- Induced Electrical current in cortical & subcortical tissue of the brain (conductor)
- Neurons become depolarized
- Action potential propagates along the neuron
- Release neurotransmitters at synapse & continues propagation of signal to other brain regions and structures

Targeted Effects on Brain Mood Circuits

Activation of fronto-cingulate brain circuit following a course of TMS applied to the left dorsolateral prefrontal cortex in patients with Major Depression

Biological and Behavioral Effects of Repeated TMS

- Outcome dependent upon stimulation parameters
- Changes in blood flow and metabolism at stimulation site
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Local GABA and glutamate effects
- Effects on thyroid hormones and HPA axis
- Evidence of neurogenesis gene induction (e.g., BDNF upregulation)
- Plasticity-like actions (i.e., Long-Term Depression/Long-Term Potentiation-like effects)
- Increase in grey matter volume and hippocampal volume
- Changes in connectivity/activity of neural circuitry (e.g., DLPFC-anterior cingulate cortex)
- TMS entrains and resets thalamocortical oscillators, normalizes regulation, and facilitates reemergence of intrinsic cerebral rhythms and through this mechanism of action restores normal brain function

TMS Field is Evolving Quickly

1985
Professor Anthony Barker & colleagues created first magnetic nerve stimulator

1990 – 2006
EARLY IMPORTANT RESEARCH

2008
First TMS device, NeuroStar® received FDA clearance for MDD

2013
First TMS device, Eneura® for migraine
TMS Field is Evolving Quickly

- **2013**: 2nd device – Brainsway® H1 coil, FDA-cleared for MDD
- **2015**: 3rd via 510 K - MagStim® for MDD
- **2016**: 4th via 510 K - MagVenture for MDD
- **2017**: 5th 510 K Cloud TMS for MDD
- **2018**: 6th via 510K Nexstim for MDD, 7th via 510 K – MAG and more for MDD
TMS Field is Evolving Quickly

- **2018**
  - MagVenture CB70
    - FDA-cleared iTBS for MDD

- **2018**
  - Brainsway® H7 Coil
    - received FDA clearance for Refractory OCD

- **2019**
  - 510K MagVenture DB80
    - for Refractory OCD

- **2020**
  - Brainsway® H4 Coil
    - FDA-cleared for Aid to Smoking Cessation
TMS Field is Evolving Quickly

Brainsway® H1 coil FDA-cleared for MDD with Anxious features

510K Neurostar for Refractory OCD

510 K – NeuroStar MDD with Anxious features

Pain?

The Future?
FDA-Cleared Devices in the United States

2008
NeuroStar
Figure 8 iron core
neurostar.com

2013
Brainsway
Hesed coil
brainsway.com

2015
Magstim
Figure 8
magstim.com

2015
MagVenture
Figure 8
magventure.com
FDA-Cleared Devices in the United States

2016
Cloud TMS
Figure 8
neurosoft.com

2017
Nexstim
NeuroNavigated
NBT
Figure 8
nexstim.com

2018
Apollo
Figure 8
magandmore.com
Neurocare
Design Depth and Width of Stimulation

FDA-cleared for:

- Treatment of MDD 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
- Treatment of OCD that has not responded to other modalities of treatment
- Augmentation of Smoking Cessation Treatment
- MDD with anxious features
- Abortive treatment for migraines

Best Practices:

- In a recurrent episodes of depression w or without anxiety, inadequately treated OCD, intractable migraines, smoking cessation that has failed standard care
- Multiple medication attempts, yet still symptomatic
- Prescribed a complex drug regimen
- Experience frequent side effects from medication

TMS: *Contraindications*

- Only absolute contraindication is 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 treatment coil
- Other concerns
  - Implanted electrodes/ stimulators
  - Deep Brain Stimulator
  - Aneurysm clips or coils
  - Cochlear implants
  - Intracranial Stents
  - Bullet or other metal fragments
  - Vagus Nerve Stimulators (per package insert vs practical implementation)

TMS Therapy Session*

- Patient is awake and alert; No anesthesia or sedation needed
- No negative effects on thinking and memory; After treatment, patients can drive or return to work
- Some patients experience headache or mild-to-moderate pain or discomfort at or near the treatment area
- None of the side effects typical with antidepressant medications

*Time, frequency of sessions varies based on device, protocol, and indication being treated
### Depression Protocols from pivotal studies

<table>
<thead>
<tr>
<th>1 - Figure 8 coils&lt;sup&gt;1&lt;/sup&gt;</th>
<th>2 - H1-Hesed coil&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LDLPFC, 120% of Motor Threshold</td>
<td>• LDLPFC, 120% of Motor Threshold</td>
</tr>
<tr>
<td>• 10 Hz (10 PPS), 4 seconds ON,</td>
<td>• 18 Hz, (18 PPS),</td>
</tr>
<tr>
<td>• 11-26 sec interval OFF</td>
<td>• 2 seconds ON,</td>
</tr>
<tr>
<td>• 75 trains</td>
<td>• 20 sec interval OFF,</td>
</tr>
<tr>
<td>• 3000 pulses</td>
<td>• 55 trains</td>
</tr>
<tr>
<td>• 5 days/wk x 6 wks = 30,</td>
<td>• 1980 pulses</td>
</tr>
<tr>
<td>• tapered w/ 6 sessions (3/wk=&gt;2/wk=&gt;1/last wk)</td>
<td>• 5 days/wk x 4 wks = 20,</td>
</tr>
<tr>
<td>• #36 Treatments in registration trial (treatment &amp; taper phase)</td>
<td>• tapered w/ 24 sessions (2 d/wk x 12 wks)</td>
</tr>
<tr>
<td>• In Randomized Controlled Trial (RCT), 9 weeks of care</td>
<td>• #44 Treatments in registration trial (treatment &amp; taper/ext phase)</td>
</tr>
<tr>
<td>• Standard covered by most insurance</td>
<td>• In RCT, 16 weeks of care</td>
</tr>
</tbody>
</table>

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<sup>1</sup> O'Reardon et al.(2007) Biol Psychiatry;  
Newer FDA cleared Depression Protocols

3- Intermittent Theta Burst\(^1\)

- Non-Inferiority trial compared to standard Figure 8 protocol in randomized clinical trial
- Triplet 50Hz bursts, 5 Hz frequency abbreviated iTBS
- 2 seconds trains (“intermittent”) ON
- 8 sec interval OFF
- 600 pulses
- 5 days/wk
- In trial, 4 weeks of care = 20 sessions
- Some insurers do not cover

4- Navigated & Accelerated intensive iTBS\(^2,3\)

- two small TCT studies w proprietarily neuro-navigated targeting & an accelerated theta burst protocol
- 3 theta burst sessions in each treatment (3 Triplet 50Hz bursts, 5 Hz frequency 2 seconds trains ON; 8 sec interval OFF) for 1800 intermittent theta bursts)
- 10 treatments/day with 50min REST between each session
- 5 days for one week = 50 longer iTBS sessions (=150 iTBS sessions in a week)
- No insurance company covers & pays

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\(^1\)Blumberger et al. 2018; \(^2\)Cole et al. 2020; \(^3\)Cole et al. 2021; www.accessdata.fda.gov
Treatment Duration

• The average number of TMS sessions is 30 with 6 tapered session when using a standard protocol
• Extending care beyond average number can convert non-responders to responders or responders to remitters\(^1, 2, 3\)
• There is significant evidence that more pulses gives better outcomes\(^1, 2, 3, 4, 5\)
• Newer accelerated protocols with multiple treatments per day over a shorter period of time are FDA cleared; the devices are not yet available, and not covered by insurance

\(^1\) Avery et al 2008; \(^2\) Yip et al. 2017; \(^3\) McDonald et al. 2011; \(^4\) Cole et al 2020; \(^5\) Cole et al 2021
TMS Therapy is Well Tolerated
Most common adverse events with all coils (incidence <5%)

TMS Side Effects
- Application site discomfort/pain
- Headache
- Referred (eye, tooth, jaw) discomfort/pain
- Insomnia
- Anxiety

No Systemic Side Effects
- Other changes in sleep
- Fatigue
- Agitation
- Blurred vision
- Dry mouth
- Weight and Appetite changes
- Sexual dysfunction
- Autonomic changes / Instability
- Gastrointestinal distress
- Tremor
- Negative changes in cognition

Most Common Adverse Events with Figure-8 TMS Coil

**Time Course of Incidence of Headache in RCT**

- **Active TMS** (n=155)
- **Sham TMS** (n=146)

**Time Course of Incidence of Application-Site Pain in RCT**

## Rare, But Serious Adverse Events Have Been Studied

### Hearing Loss
- Small # of adults have experienced transient increase in auditory threshold and in RCT, 1 patient had permanent threshold shift (did not wear earplugs with H1 coil)
- Most studies report no hearing changes after TMS (with hearing protection)
- All persons in treatment room are recommended to use earplugs (min standard of 30dB protection)

### Treatment-Emergent Mania
- Early pooled data from treating MDD and depressed Bipolar patients reported treatment emergent mania was 0.84% for active treatment group (less for sham)
- Difference was not statistically different unipolar patients = 0.34% for bipolar patients = 3.1%

### Treatment-Emergent Suicidal Ideation
- Treatment emergent disease exacerbation
- Population with increased severity of clinical condition
- Commonly reported event in RCT
  - 1.9% with sham*
  - 0.6% active TMS
*1 non-lethal OD in sham group

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Seizure is the most serious side effect associated with TMS.
The risk of seizures is <0.1% per treatment course.
TMS and Seizures

• 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 is very low

• The risk is less than or comparable to risk of seizure associated with antidepressant medications

• TMS induced seizures occur primarily during treatment session itself; seizures could happen while calibrating a dosage (finding MT); no sequelae and no progression to epilepsy

Large-Scale RCTs

- Four (4) large-scale studies (sample sizes >100), 3 studies patients took no medications and in 1 study patients took medication concurrently
  - Two (2) large multicenter industry supported trials that led to FDA approval for two devices; remainder of devices were cleared with 510K clearances
  - NIH-funded study with dosage parameters similar to those in the industry-sponsored study but with sham design enhancements
  - European study of the augmentation effects of TMS when used in combination with pharmacotherapy

RCT = randomized controlled trial

Evidence for Efficacy of TMS for MDD

- 35+ clinical trials in adults
- Numerous meta-analyses
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increased intensity
  - Increased pulse number
- Large meta-analysis in 2010\(^1\)
  - 34 individual trials, 1383 patients
  - Found TMS to have \textbf{large effect size of 0.55}

\(^1\)Slotema CW, et al. \textit{J Clin Psychiatry}. 2010
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
Remission is Possible with TMS Therapy: 1 in 2 Patients Respond, 1 in 3 Achieve Remission

Long-Term Phase Results (12 Months)

Outcomes measured 1 year following acute treatment

- Physician directed standard of care
- 36.2% of patients received TMS reintroduction
- Average # of TMS sessions during year = 16

Why are real world results better than clinical trial results?

- Combination Strategies
  - Well-tolerated with many medications
  - Psychotherapy and Behavioral Activation

- Patients who enroll in studies may not reflect clinical populations in a variety of ways

- Engagement in Life
  - Intensive Outpatient Program
  - Routine
  - Positive Human Interaction

After Acute Treatment of Depression

- Goal is remission and to maintain
- We know reintroduction works with TMS, often just a few TMS sessions or clustered sessions can help a patient regain previous response/remission
- Maintenance TMS is not covered by most payors and evidence is lacking
- With most payor policies, TMS may not covered again if the patient relapses within 2-3 months
- Next options, may have more 'costs', more side effects, and less durability
Conclusion

• TMS is non-invasive form of brain stimulation based principles of electromagnetic induction from early 1800s
• TMS is a safe and effective treatment of moderate-to-severe MDD
• Additional FDA-cleared indications besides Major Depressive Disorder:
  ▪ migraine (single pulse)
  ▪ refractory OCD
  ▪ smoking cessation,
  ▪ comorbid anxiety symptoms in adult patients with MDD
• there is emerging research supporting its efficacy in treatment of other neuropsychological disorders
• TMS is well-tolerated and without risks of systemic side effects
• TMS should be considered a treatment option for patients with MDD who do not benefit sufficiently from medications to reduce the burden and disability of MDD
Need More CME?

Educational CME Courses

• CTMSS CME course, PULSES: Introductory course on TMS, 16-hour CME program with Hands-on Device Training. 3–4 courses/year, both US and International locations, [www.clinicaltmssociety.org](http://www.clinicaltmssociety.org)

• CTMSS Annual Education Meeting: 2 days on Advanced TMS topics – in Colorado Springs, CO this year; London UK in 2024

University-Based Training Courses

• Medical University of South Carolina

• Berenson-Allen Center for Non-Invasive Stimulation (MGH-Harvard)

• Duke University Medical Center

There are also industry-based courses
Need More – Self Study?

Textbooks

• Fitzgerald PB & Daskalakis ZJ. *rTMS Treatment for Depression*. Springer Cham Publishing; 2022.

Consensus Statements for TMS for Depression

Want to Connect to Like-Minded Colleagues?

- Join Clinical TMS Society, [www.clinicaltmssociety.org](http://www.clinicaltmssociety.org)

- Join American Psychiatric Association Caucus on Neuromodulation, next meeting at APA meeting:
  - Date: Monday, May 22, 2023
  - Time: 3:30 PST - 5:00 PM PST
  - San Francisco Marriott Marquis, Room: Golden Gate C1

- Celebrate and give Tribute to Mark S. George, Recipient of the APA Research Award 2023
  - Date: Monday, May 22, 2023
  - Time: 6:00 PM - 8:00 PM
  - Minna Gallery, 111 Minna Street, San Francisco, CA 94105
Special Thanks

to Clinical TMS Society (CTMSS) members:

- Kimberly Cress, MD
- Randy Pardell, MD, DLFAPA
- Suzanne Kerns, MD
- Kristin Raj, MD
- Ira Mania, MD
- Bob Sammons, MD
- Linda Carpenter, MD
- Mohamed Abdelghani, MBBCh, MSc, MRCPsych
- Mark S. George, MD
- Carlos Lowell, DO & Debra Stultz, MD and other members of the CTMSS Outreach & Education Committees and the CTMSS administrative team at The Exchange
slides that follow are for Q & A section only
TMS for MDD with Anxious Features
Newest Indication, August 2021

- H1 coil initially cleared for MDD in 2013 recently FDA approved for MDD with Anxious Features
- Pending publication, retrospective analysis from RCTs and open-label data presented to FDA
- and obtained clearance for MDD with comorbid anxiety
Efficacy for Treatment of Refractory OCD with TMS Therapy
OCD
Three devices FDA-cleared

- Large coils unique for OCD
- Combined Exposure treatment (ERP-like provocation) with OCD therapy
- Some payor coverage

ERP = Exposure and Response Prevention
Hyperactive Cortico-Striato-Thalamo-Cortical (CSTC) Loop Circuits

Dougherty DD, et al. JAMA Psychiatry. 2018
A Neurochemical Explanation of Hyperactive CSTC Circuit

Hyperactive CSTC Circuits
- Decreased “Breaks”
- Increased “Acceleration”

“Breaks” in OCD – Diminished serotonergic and GABAergic activities in midbrain (raphe nuclei) and mPFC interneurons

“Acceleration” in OCD – Increased glutaminergic and dopaminergic activities in cortical, striatum, and thalamus

mPFC = medial prefrontal cortex.
Treatment Modalities for OCD

**Medications** (chemical neuromodulation)
SSRIs, SNRIs, TCAs, plus augmentation agents

**Psychotherapy** (behavioral neuromodulation)
Cognitive-Behavioral Therapies like DBT (Dialectical Behavioral Therapy), ERP (Exposure and Response Prevention), and ACT (Acceptance and Commitment Therapy)

**Neurostimulation** (“electrical” neuromodulation)
DBS (Deep Brain Stimulation), rTMS (initially, TMS deep or “broad” repetitive Transcranial Magnetic Stimulation, later with large figure 8 coils, then more recently with Figure 8 coils)

**Psychosurgery**
Anterior Cingulotomy, Anterior Capsulotomy, Subcaudate Tractotomy
OCD Treatment Challenges

• Many (40%–60%) patients do not show clinically meaningful response to an SSRI, with only one-third showing response after switching to another SSRI\textsuperscript{1,2}

• Other treatment strategies, including augmentation with medication (antipsychotics) and Cognitive-Behavioral Therapies like DBT, ERP, and ACT, may help, but many patients remain symptomatic and impaired

• Same limitations with medication side effects as those reviewed with the treatment of depression

• Psychosurgery comes with risk of severe complications

Targets Varied in Early Studies

- Meta-analysis showed SMA (supplementary motor area) as best target (directly above sgACC)
- For treatment, coil placed 4 cm anterior to the motor spot and aligned symmetrically over the mPFC
- Dosage determined (Motor Threshold) over Right foot

sgACC = subgenual anterior cingulate cortex.
Carmi L, et al. *Brain Stimul.* 2018
Studies included Symptom provocation (ERP):
“For each patient, a list of personalized provocations was designed by a clinician during the first assessment meeting. These provocations were designed to achieve a self-report score between 4 and 7 on a 1 to 10 visual analog scale (VAS) and were recorded on the case report forms (CRFs). Following each treatment, participants were allowed to perform any relevant ritual they desired.”
**Outcome**

- Predefined response criteria (ie, 30% reduction in YBOCS relative to baseline)
- In HF group (7/16; 43.75%) and in sham group (1/14; 7.14%) ($P<.05$)
- Using the more restrictive criteria of 35% to calculate response rate
- In HF group (5/16; 29.41%) and in sham group (1/14; 7.14%) ($P<.10$)

**Limitations**

- Relatively small sample size
- Effect of provocation was not controlled
- Relevant brain activity was not recorded during the provocation
- Extent to which the ACC and the mPFC were adequately stimulated needs to be further investigated
- Varying RMT intensities (100%–110%)
- Total number of pulses administered, was different between the LF group (22,500 pulses) and HF group (50,000 pulses)

**Suggestion for Clinical Practice**

- FDA clearance

30% Reduction in YBOCS Relative to Baseline

TMS for OCD

**P<.01**

*P<.05

***P<.001

Carmi L, et al. *Brain Stimul.* 2018
More Recent RCT Study
TMS for OCD

- Prospective multicenter randomized Double-Blind Sham-Controlled Trial
- **Aim**: To examine the therapeutic effects of dTMS (H7 coil) on OCD symptoms
- **Number treated**: 99 participants

**Protocol**
- HF (20 Hz) at 100% of RMT or sham dTMS to mPFC-ACC bilaterally for 6 weeks
- 2 second trains (20 pps) and 20 seconds ITI for a total of 50 trains (2000 pulses)
- TMS after symptom provocation

Hz = PPS = pulses per second; ITI = intertrial interval.
Second RCT TMS for OCD

Visual representation of improvement by % change of YBOCS of individual patients

FIGURE 2. Change from baseline in mean YBOCS score through the study for the active and sham dTMS treatment groups.

- Sham treatment
- Active treatment

Change From Baseline in YBOCS Score

Baseline | Week 2 | Week 3 | Week 4 | Week 6 | Follow-up
--- | --- | --- | --- | --- | ---
47 | 45 | 41 | 42 | 40 | 43
47 | 41 | 41 | 38 | 43 | 40

\(^a\) dTMS = deep repetitive transcranial magnetic stimulation; YBOCS = Yale-Brown Obsessive Compulsive Scale. Each data point includes the patients with recorded YBOCS scores at that time point.

**Second RCT**
**TMS for OCD**

**Outcome**
- Reduction in YBOCS score of among 6.0 points in patients who received active dTMS vs 3.3 points in sham treatment
- **Effect Size: 0.69**
- Response rate post treatment: of 38.1% (16/42) in active dTMS group vs 11.1% (5/45) in sham group ($P=.003$)
- Response rate at the 1-month follow-up: 45.2% (19/42) in the active dTMS group vs 17.8% (8/45) in the sham treatment group ($P=.006$)

**Limitations**
- Relatively small sample size
- Effect of provocation was not controlled
- Functional brain imaging was not done to measure the extent which mPFC and ACC stimulation

**Suggestion for Clinical Practice**
- FDA Clearance

TMS for Smoking Cessation
Addiction, General Mechanism

• Addiction is a brain disease but none of our current treatments directly target known brain circuits involved in addiction

• Many TMS studies have shown the ability to reduce cue-induced craving in the lab (ETOH, smoking, cocaine, methamphetamine, food in anorexia)

• Open-label rTMS studies have shown potential clinical reduction in substance use over the short-term for addiction

• A recent RCT showed reduction of smoking and improvement in depression and anxiety, with continued smoking reduction at 3 months

• Brainsway® had FDA pivotal trial for adjunctive aid in short-term smoking cessation

Brain Targets in Addiction

Image from NIDA website
Results

- Greater abstinence at 2nd week
- Overall, no sustained effect
- Limited effect on craving

RCT blinded, placebo-controlled 2 weeks of active rTMS 10 sessions with NRT and 4-week follow-up with NRT alone and assessed at 6, 12 weeks

NRT = nicotine replacement therapy.
**TMS as an Aid in Smoking Cessation**

- RCT, double-blind, placebo-controlled
- **Aim**: to evaluate the safety and efficacy of dTMS as an aid in smoking cessation in heavy smokers
- **Number treated**: 262 enrolled in multicenter study and 168 completed the study (3 weeks treatment and 3 weeks of follow-up)
- **Primary end point** was 4-week Continuous Quit Rate (CQR)

TMS as an Aid in Smoking Cessation

**Protocol**

- Brainsway’s proprietary H4 coil
- 5 treatments/week for 3 weeks then 1 treatment/week for 3 weeks (Total 18)
- 10 Hz 120% SMT, 3 s (30 pulses), 15 sec IPI (inter-pulse interval); total of 1800 pulses
- H4 stimulation site: IPFC and insula
- Cue induced craving (5-minute provocation procedure imagining greatest trigger) with audio script and viewing pictures of smoking
- Then TMS
- Afterwards 2-minute motivational talk was read

Brainsway® H4 Coil FDA-Cleared as an Aid in Smoking Cessation

**Outcome**

- CQR was 28.4% in the treatment group vs 11.7% in the sham group ($P=.0063$)
- ITTQR was 17.1% in the treatment group vs 7.9% in the sham group ($P=.0238$)
- A secondary end point; reduction in the number of cigarettes smoked

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Active</th>
<th>Sham</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average # smoked/week</td>
<td>132</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>After 3 weeks treatment</td>
<td>38</td>
<td>57</td>
<td>$P=.0018$</td>
</tr>
<tr>
<td>After 6 weeks of the study</td>
<td>31</td>
<td>48</td>
<td>$P=.0125$</td>
</tr>
</tbody>
</table>

**Limitations**

- Current medication therapies show quit rates at 6 months:
  - NRT Patch, 23%
  - Varenicline, 24%
  - NRT Patch + Lozenges, 27%

TMS Insurance Coverage

- TMS has coverage in every state for MDD; likely will take a few years for OCD & migraine & smoking cessation
- TMS for severe MDD is covered by most major private insurance companies
  - Policies vary; most require 1-6 antidepressant failures
  - +/- Psychotherapy failure
  - Covered by Medicare for Depression in every state in US

Over 300 million Covered Lives
TMS is Included in MDD Practice Guidelines
First line & after medication failure(s)

Since 2010, American Psychiatric Association has included TMS in guidelines: “…acute phase treatment may include pharmacotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy, transcranial magnetic stimulation or light therapy…”

Since 2009
World Federation of Societies for Biological Psychiatry

Since 2009
Canadian Network for Mood and Anxiety Treatments

Since 2010,
Institute for Clinical Systems Improvement

TMS for Migraine
Migraine
one device FDA cleared

- This device uses single TMS pulse to “abort migraine” and prevent migraine
- Limited risk
- Low adaptation by neurologists in clinical practice
- Limited Payor coverage
- Recently re-engineered
- www.eneura.com

sTMS mini

eNeura FDA Clearance, September 7, 2017
Single Pulse TMS for Migraine

- Portable, battery-operated device generates a 0.9T pulse lasting less than a millisecond
- FDA cleared for abortive acute treatment in migraine with aura in December 2013
- FDA cleared in September 2017 for acute and preventative treatment of migraine headaches in adolescents (age 12 and older) and adults
Single Pulse TMS for Migraine

- **Protocol**
  - Single Pulse TMS over occiput
  - Participants were instructed to treat up to 3 attacks over 3 months while experiencing aura

- **Double blind RCT at 18 centers in the USA**
- International criteria for migraine with aura was used, with visual aura preceding at least 30% of migraines followed by moderate or severe headache in more than 90% of those attacks
- **Aim:** To test efficacy & safety of sTMS for acute treatment of migraine with aura
- **Number treated:**
  - 201 Participants were randomly allocated to sTMS (n=102) or sham (n=99).
  - 164 participants treated at least 1 attack with sTMS (n=82) or sham stimulation (n=82)

Lipton et al. 2010
Single Pulse TMS for Migraine

**Outcome:**
- Pain-free response rates after 2 h were significantly higher with sTMS (32/82 [39%]) than with sham stimulation (18/82 [22%]). Therapeutic gain of 17% (95% CI 3–31%; $p=0.0179$).
- Sustained pain-free response rates significantly favored sTMS at 24h and 48h post-treatment.
- Non-inferiority was shown for nausea, photophobia, and phonophobia.
- No device-related serious adverse events were recorded, and incidence and severity of adverse events were similar between sTMS and sham groups.

**Suggestion for Clinical Practice:**
- FDA clearance

Lipton et al. 2010
Single Pulse TMS for Migraine

Lipton et al. 2010

Figure 2: Pain-free response at 2 h, 24 h, and 48 h on active and sham treatment
sTMS=single-pulse transcranial magnetic stimulation. Error bars=SE.
Single Pulse TMS for Migraine Prevention

- Multicenter, prospective, single arm, open label, observational study
- Inclusion criteria: ≥ 4 headaches a month of at least ≥ 4 hours duration each
- **Aim:** Test the efficacy and tolerability of sTMS for migraine prevention.
- **Number treated:**
  - 263 consented; 132 met inclusion criteria (treated)
  - 95 completed full treatment protocol

**Protocol**

- **Single Pulse TMS**
  - Preventative treatment: 2 pulses, 15 mins rest, followed by another 2 pulses twice per day
  - **Acute treatment:** 3 consecutive pulses; if no symptom relief in 15min then the dose could be repeated up to twice (9 total)
  - Participants were allowed rescue medication 30 mins after the first 3 pulses were delivered

Starling et al. 2018
Single Pulse TMS for Migraine Prophylaxis

**Outcome:**
- Baseline rate of 9 headache days a month was reduced by 2.75 days ($p < 0.0001$)
- 46% of patients experienced a 50% or greater reduction in headaches

**Limitations:**
- Not RCT, prospective, open label study
- Medication overuse was not analyzed
- Heterogenous sample (i.e. with different types of Migraine)
- Sample was mainly Caucasian women

**Suggestion for Clinical Practice:**
- FDA Clearance