Neuromodulation Techniques: State of the Science

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Today's Speakers

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Objectives

- Discuss the need for alternative treatments in depression and the evolution of neuromodulation
- Consider examples of invasive neuromodulation techniques, such as deep brain stimulation and vagus nerve stimulation
- Consider examples of noninvasive neuromodulation techniques, including transcranial magnetic stimulation and electroconvulsive therapy

The Need for Alternative Treatment Options in Depression

- MDD is widespread, with an estimated lifetime prevalence of 15% and an annual incidence of ~7%[1]
  - The disorder is associated with significant loss of work productivity, life expectancy, and quality of life[1]
- Depression is a heterogeneous disorder, with variable medication responses and tolerability across patients[1]
  - The STAR*D study suggested that even with up to 4 aggressive treatment strategies, ~30% of patients would not achieve remission[2*]

Patients with Major Depressive Disorder that received 1 to 4 successive treatment steps in STAR*D[2]

*Overall cumulative remission rate based on assumption that all patients stayed in treatment and those who exited had similar remission rates to those who stayed in treatment.

MDD, major depressive disorder; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

1. Ceskova E, et al. *Neuropsychiatr Dis Treat*. 2018;14:741-747.
2. Rush AJ, et al. *Am J Psychiatry*. 2006; 163:1905-1917.

Polling Question

Which of the following best describes your perception of neuromodulation techniques (eg, electroconvulsive therapy)?

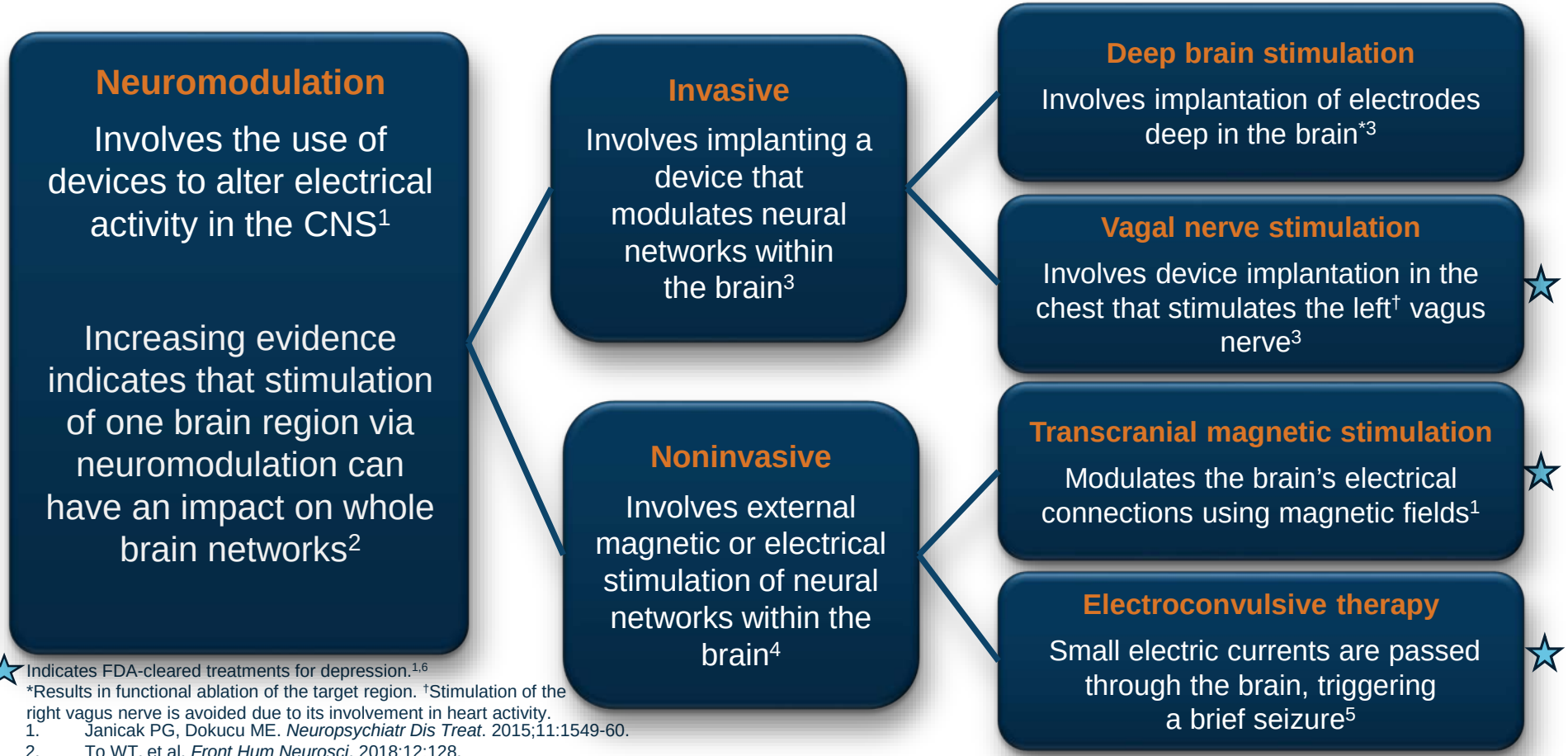
A. I don’t have much experience with neuromodulation
B. They are important for the treatment of some patients
C. They are treatments of last resort
D. Their benefits generally don’t outweigh their risks

The Brain as a Neural Network

- A recent paradigm shift has led to a increased focus on neural interactions and connectivity rather than on local effects of particular brain region alterations[1,2]
- The human brain is conceptualized as a complex network of interconnected regions[2]
  - Dysfunction can spread easily between connected elements
  - Behavioral manifestations of psychiatric diseases are believed to be the result of alterations in the brain network and its connectivity

1. Andrade et al. *Int J Clin Neurosci Ment Health.* 2017; 4(Suppl. 3):S07.
2. To WT, et al. *Front Hum Neurosci*. 2018;12:128.

Neuromodulation Examples



Indicates FDA-cleared treatments for depression.[1,6]

*Results in functional ablation of the target region. †Stimulation of the right vagus nerve is avoided due to its involvement in heart activity.

1. Janicak PG, Dokucu ME. *Neuropsychiatr Dis Treat*. 2015;11:1549-60.
2. To WT, et al. *Front Hum Neurosci*. 2018;12:128.
3. Fogwe DT, Mesfin FB. *Neuromodulation, Surgery For Psychiatric Disorders*. 2018 Jan 19. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-. Available from http://www.ncbi.nlm.nih.gov/books/NBK482366/.
4. Hu YP, et al. *Curr Behav Neurosci Rep*. 2015;2(3): 173-185.
5. Mayo Clinic. Electroconvulsive therapy (ECT). Available at: https://www.mayoclinic.org/tests-procedures/electroconvulsive-therapy/about/pac-20393894. Accessed June 2018.
6. Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses: Draft Guidance for Industry, Clinicians and Food and Drug Administration Staff. Available at: https://www.fda.gov/downloads/MedicalDevices/.../UCM478942.pdf. Accessed June 2018.

Vagus Nerve Stimulation

Introduction

Background

- VNS was originally used to treat treatment-resistant epilepsy and was cleared for treatment-resistant depression in 2005[1]

Procedure

- A pulse generator is implanted in the chest and electrodes implanted on the left vagus nerve* administer a small electrical pulse in regular intervals[1,2]

Patient Population

- Studied in more advanced stages of treatment-resistant depression (many failed ECT)[3,4]

*Stimulation of the right vagus nerve is avoided due to its involvement in heart activity.[2]
ECT, electroconvulsive thearpy; VNS, vagus nerve stimulation.

1. Milev RV et al., *Canadian J Psychiatry.* 2016;61(9):561-75.
2. Fogwe DT, Mesfin FB. *Neuromodulation, Surgery For Psychiatric Disorders*. 2018 Jan 19. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-. Available from http://www.ncbi.nlm.nih.gov/books/NBK482366/.
3. Rush AJ et al., *Biol Psychiatry.* 2005;58:347-54.
4. Aaronson ST et al., *Am J Psychiatry.* 2017;174(4):640-8.

Vagus Nerve Stimulation
Efficacy and Safety

Efficacy

- A randomized, sham-controlled trial explored the efficacy of adjunctive VNS in 235 patients experiencing an episode due to major depressive disorder (n=210) or the depressed phase of bipolar disorder (n=25)[1]
  - At 10 weeks, the difference in response rate* between the two groups was non-significant (15.2% active vs 10.0% sham)
  - However, a 12 month naturalistic follow-up study found that treatment with VNS significantly improved response and remission rates* from 3 months to 12 months of treatment[2]
- A 5 year, observational study found that, compared to treatment-as-usual (n=301), adjunctive VNS (n=494) had significantly higher 5-year cumulative response (67.6% vs 40.9%) and cumulative remission (43.3% vs 25.7%) rates†[3]

Safety

Side effects can include hoarse voice, cough, dyspnea, pain, anxiety, nausea and difficulties swallowing[1,2]

*Criteria for response: ≥50% decrease in HAM-D-24 score from baseline; criteria for remission: HAM-D-24 score ≤9. †Criteria for response: ≥50% decrease in MADRS score from baseline; criteria for remission: MADRS score ≤9.
HAM-D-24, 24-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; VNS, vagus nerve stimulation.

1. Rush AJ et al., *Biol Psychiatry.* 2005;58:347-54.
2. Rush AJ et al., *Biol Psychiatry.* 2005;58:355-63.
3. Aaronson ST et al., *Am J Psychiatry.* 2017;174(4):640-8.

Deep Brain Stimulation
Introduction

Background

- DBS has been used successfully for the treatment of Parkinson's disease since the 1980's[1]

Procedure

- Unilateral or bilateral electrodes are implanted in the brain and connected to a battery-powered neurostimulator implanted in the chest area[1]

Patient Population

- Because of the risks of neurosurgery and its experimental nature, DBS has been primarily studied in severely depressed patients who did not respond to antidepressants or ECT[1-3]

DBS, deep brain stimulation; ECT, electroconvulsive therapy.

1. Pandurangi AK et al., *Asian J Psychiatr.* 2012;5:3-10.
2. Lozano AM et al. *Biol Psychiatry.*2008;64:461-7.
3. Holtzheimer PE et al. *Lancet Psychiatry.* 2017;4:839-49.

Deep Brain Stimulation

Efficacy and Safety

Efficacy

- Major studies of DBS in TRD have generated mixed results[1,2]
- In a study of 20 patients with TRD, DBS of the subcallosal cingulate gyrus (SCG) led to response and remission rates of 55% and 35%, respectively at 12 months[1*]
- More recently, a prospective, randomized, sham-controlled trial of DBS of SCG in TRD found no significant difference in response rate between sham (n=30) and active (n=60) treatment during the 6 month, double-blind phase of the trial[2]

Safety

- The most common adverse events are related to surgical placement of the device and include post-operative edema, surgical site pain, and infection[1-3]

*Response was defined as a ≥50% reduction in HRSD-17 baseline score. Remission was defined as a score of ≤7 on the HRSD-17.
DBS, deep brain stimulation; HDRS-17, 17-item Hamilton Depression Rating Scale; TRD, treatment-resistant depression.

1. Lozano AM et al. *Biol Psychiatry.*2008;64:461-7.
2. Holtzheimer PE et al. *Lancet Psychiatry.* 2017;4:839-49.
3. Pandurangi AK et al., *Asian J Psychiatr.* 2012;5:3-10.

Electroconvulsive Therapy

Introduction

Background[1,2]

- ECT dates back to the 1930s and the stigma attached to this technique is largely based on early treatments, where high doses of electricity were administered without anesthesia, with the potential for serious side effects

Procedure[1,2]

- Electricity is delivered directly to the brain via scalp electrodes to induce a generalized tonic-clonic seizure under general anesthesia with muscle relaxation

Used to Treat[2]

- Severe and/or treatment-resistant depression
- Severe and/or treatment-resistant mania
- Severe and/or treatment-resistant psychosis
- Catatonia

ECT, electroconvulsive therapy.

1. Deng ZD, et al. *Curr Opin Neurobiol*. 2015;30:38-43.
2. Mayo Clinic. Electroconvulsive therapy (ECT). Available at: https://www.mayoclinic.org/tests-procedures/electroconvulsive-therapy/about/pac-20393894. Accessed June 2018.

Electroconvulsive Therapy

Efficacy and Safety

Efficacy

- The modern version of ECT is considered the “gold standard” brain stimulation treatment for severe MDD[1]
- In the treatment of depression, ECT can result in response rates of 70-80% and remission rates of 40-50% or higher[2]
- One study evaluating the efficacy of right unilateral ultrabrief pulse ECT combined with an SNRI for the treatment of geriatric depression found that 61.7% (148/172) of patients remitted (HAM-D score ≤10) after an acute course of treatment[3]
- Electrode placement and other stimulation parameters contribute to efficacy as well as adverse events and are areas of ongoing research[1]

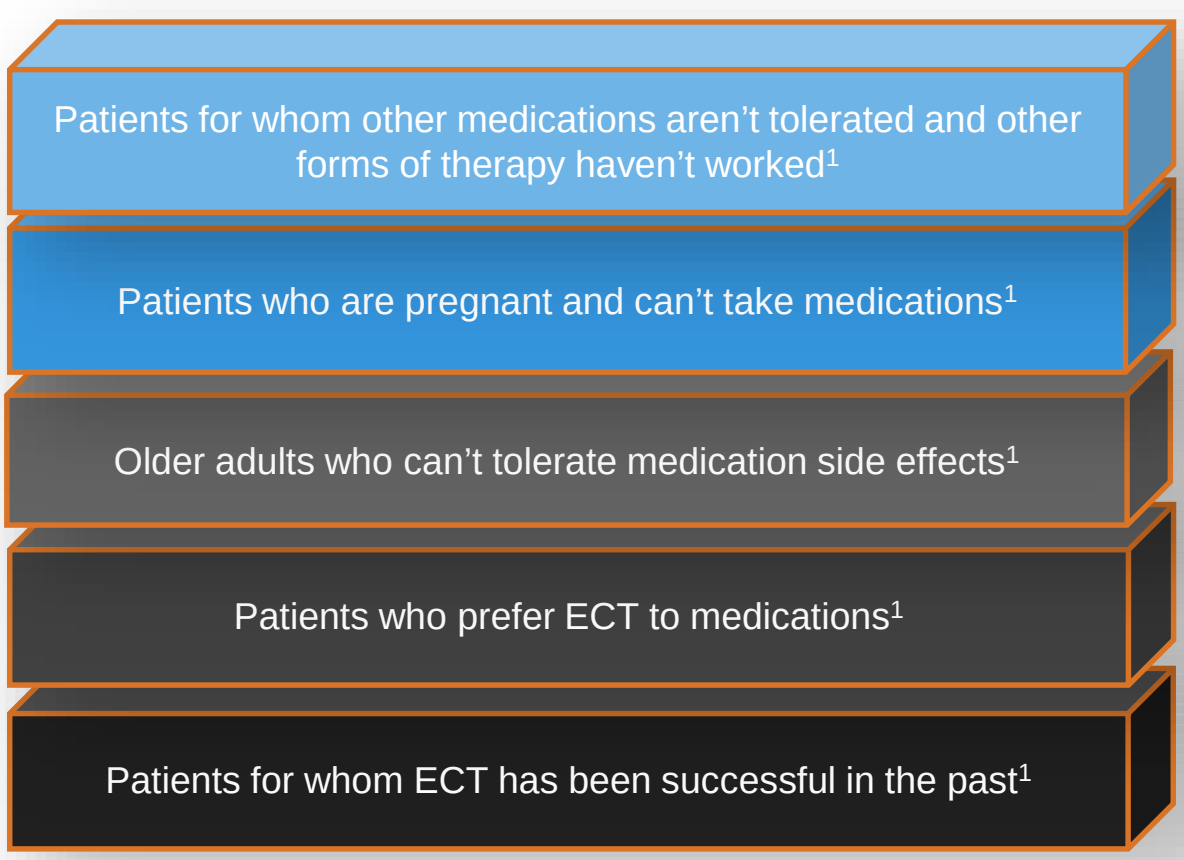
Safety

- Adverse cognitive effects, which can reduce tolerability can include post-ictal disorientation, learning and memory difficulties, and retrograde amnesia[1]

ECT, electroconvulsive therapy; HAM-D, Hamilton depression scale; MDD, major depressive disorder.

1. Deng ZD, et al. *Curr Opin Neurobiol*. 2015;30:38-43.
2. Milev RV et al., *Canadian J Psychiatry.* 2016;61(9):561-75.
3. Kellner CH et al., *Am J Psychiatry.* 2016;173(11):1101-9.

Patients Who May Be Candidates for Electroconvulsive Therapy



Use may be limited by[2]

- Lack of access in some areas
- Adverse cognitive effects
- Substantial relapse rates after successful acute treatment course
- Negative public image

ECT, electroconvulsive therapy.

1. Mayo Clinic. Electroconvulsive therapy (ECT). Available at: https://www.mayoclinic.org/tests-procedures/electroconvulsive-therapy/about/pac-20393894. Accessed June 2018.
2. Janicak PG, Dokucu ME. *Neuropsychiatr Dis Treat*. 2015;11:1549-60.

Transcranial Magnetic Stimulation

Introduction

Background[1]

- In 2008, FDA cleared the first TMS device for therapeutic clinical use in MDD (focal iron core coil)
- Additional devices have been subsequently cleared

Procedure[1]

- A non-invasive, stimulating magnetic field is used to induce electrical currents in spatially discrete regions of the cerebral cortex, with a peak magnetic strength similar to that produced by an MRI device
- Pulses can be delivered at high (10–20 Hz; excitatory) or low frequencies (≤1 Hz; inhibitory)
- The most common procedure for depression involves high frequency pulses administered over the left DLPFC

Indications

- Cleared for treatment-resistant depression[1]
- Under investigation*: pain, schizophrenia, addiction[2]

*Not a complete list

DLPFC, dorsolateral prefrontal cortex; FDA, Food and Drug Administration; MDD, major depressive disorder; MRI, magnetic resonance imaging; TMS, transcranial magnetic stimulation.

1. Perera T, et al. *Brain Stimul*. 2016;9(3):336-346.
2. Bermudes RA et al., *Transcranial Magnetic Stimulation.* Arlington, VA: APA Publishing. 2018.

Transcranial Magnetic Stimulation

Efficacy and Safety

Efficacy

- A double-blind, multisite, sham-controlled study in 301 medication-free patients with treatment-resistant MDD* investigated the efficacy of left DLPFC TMS in the treatment of a depressive episode:
  - Compared to the sham group, patients who received active TMS showed a significant improvement in HAMD17 scores from baseline at 4 and 6 weeks (p=0.006, p = 0.005, respectively)[1]
  - A NIMH sponsored study using similar parameters found active TMS to be significantly more likely than sham to induce remission[2]
- An additional study of a deep TMS device (H-coil) in TRD* found that after 16 weeks of treatment† response rates were 44.3% vs 25.6% and remission rates‡ were 31.8% vs 22.2%, for active TMS vs sham, respectively[2]

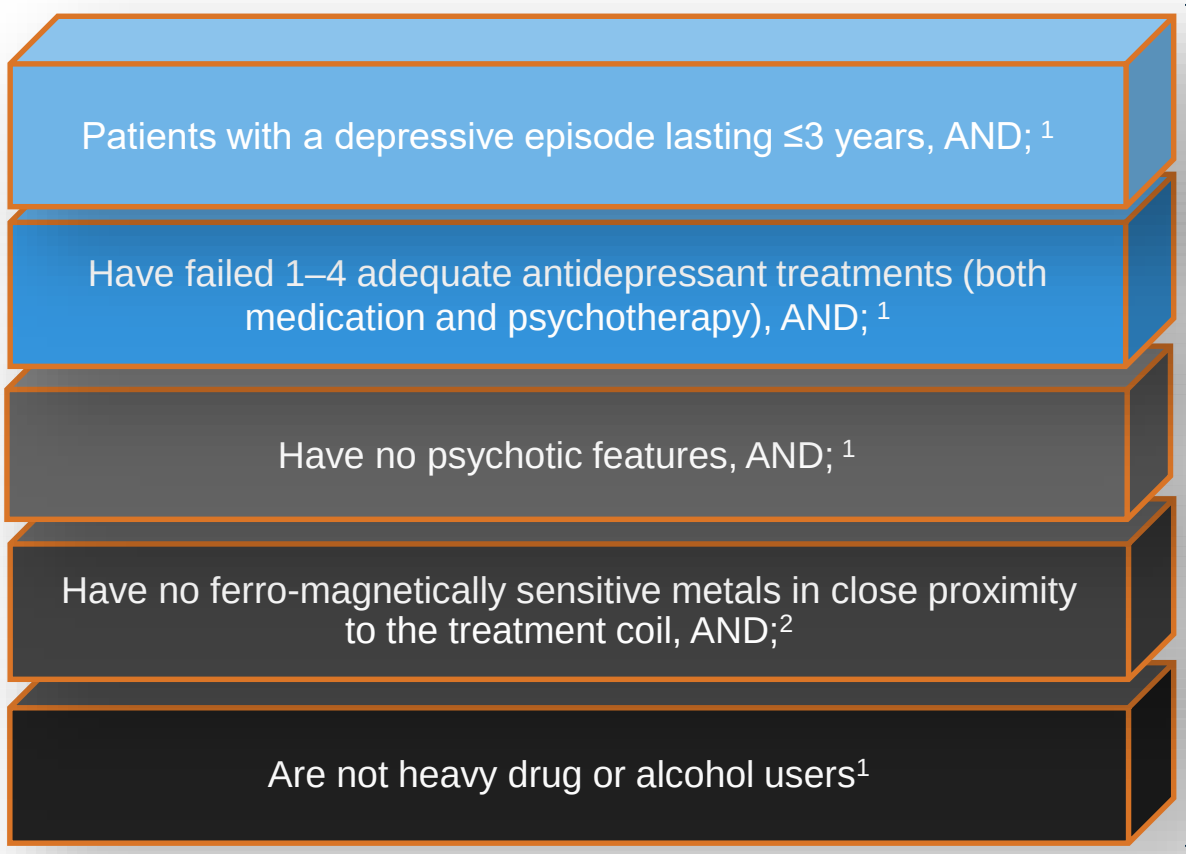
Safety

- Adverse events are generally mild and limited to transient scalp discomfort or pain[1,3]
- Seizures are a rare risk of TMS[3]

*At least 1, but no more than 4 failed antidepressant treatments. †5 treatments weekly for 4 weeks followed by 2 treatments weekly for 12 weeks. ‡Response was defined as a ≥50% reduction from baseline in HAMD21 scores; remission was defined as a HAMD21 score <10.
DLPFC, dorsolateral prefrontal cortex; HAMD17, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; HAMD21, 21-item Hamilton Depression Rating Scale; TMS, transcranial magnetic stimulation; TRD, treatment-resistant depression.

1. O'Reardon JP et al., *Biol Psychiatry.* 2007;62:1208-1216.
2. Bermudes RA et al., *Transcranial Magnetic Stimulation.* Arlington, VA: APA Publishing. 2018.
3. Perera T, et al. *Brain Stimul*. 2016;9(3):336-346.

Patients Who May Be Candidates for Transcranial Magnetic Stimulation (TMS)



Should not be used to treat patients who have:[3]

- Cochlear implants
- Aneurysm clip
- Heart/vascular clip
- Intracranial metal prothesis

TMS, transcranial magnetic stimulation.

1. Janicak PG, Dokucu ME. *Neuropsychiatr Dis Treat*. 2015;11:1549-60.
2. McClintock SM, et al. *J Clin Psychiatry.* 2018;79(1):16cs10905.
3. Andrade et al. *Int J Clin Neurosci Ment Health.* 2017; 4(Suppl. 3):S07.

Clinical TMS Society Treatment Recommendations for TMS Therapy for MDD

RECOMMENDATIONS[1]

- TMS therapy is recommended for the acute treatment of treatment-resistant depression in the indicated patient population*
- TMS therapy is recommended for use as a subsequent option for patients who previously benefitted from an acute treatment course and are experiencing a recurrence
- TMS therapy can be administered with or without concomitant antidepressant or other psychotropic medications
- TMS therapy can be used as a continuation or maintenance treatment for patients who benefit from an acute course
- TMS therapy can be reintroduced in patients who are relapsing into depression after initially responding to TMS treatment

Left prefrontal rTMS repeated daily for 4–6 weeks is an effective and safe treatment in adult patients with unipolar MDD that have failed ≥1 adequate antidepressant trials[1]

For additional guidelines, see the Consensus Recommendation for the Clinical Application of rTMS in the Treatment of Depression from the National Network of Depression Centers[2]

*Consider for patients with a DSM-5-defined clinical diagnosis of MDD, single or recurrent episode, or equivalent nosology for whom antidepressant medication has not provided a satisfactory clinical benefit, or for whom intolerance to medications precludes their use.

DLPFC, dorsolateral prefrontal cortex; DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, major depressive disorder; rTMS, repetitive TMS; TMS, transcranial magnetic stimulation.

1. Perera T, et al. *Brain Stimul*. 2016;9(3):336-346.
2. McClintock SM, et al. *J Clin Psychiatry.* 2018;79(1):16cs10905.

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Questions

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Closing

Upcoming Virtual Fora*

Event	Speaker(s)	Date	Time
Measurement-Based Care in Psychiatry: Clinical & Administrative Perspectives	• Charlotte Ostman, BA, MSW • James Greer, MD	July 25, 2018	12:00pm ET
Introducing RASP: Relapse Assessment in Schizophrenia Patients	• Heidi Waters, MBA, PhD	August 8, 2018	12:00pm ET
An Update from NCQA©: Focus on HEDIS® Behavioral Health Measures	• Junqing Liu, PhD, MSW • Lauren Niles, MPH • Nora Fritz, BA	August 22, 2018	12:00pm ET

*Register for these programs at https://www.PsychU.org/events

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