

NeuroStar[®] Transcranial Magnetic Stimulation (TMS) Therapy for Major Depressive Disorder

What are the Questions?

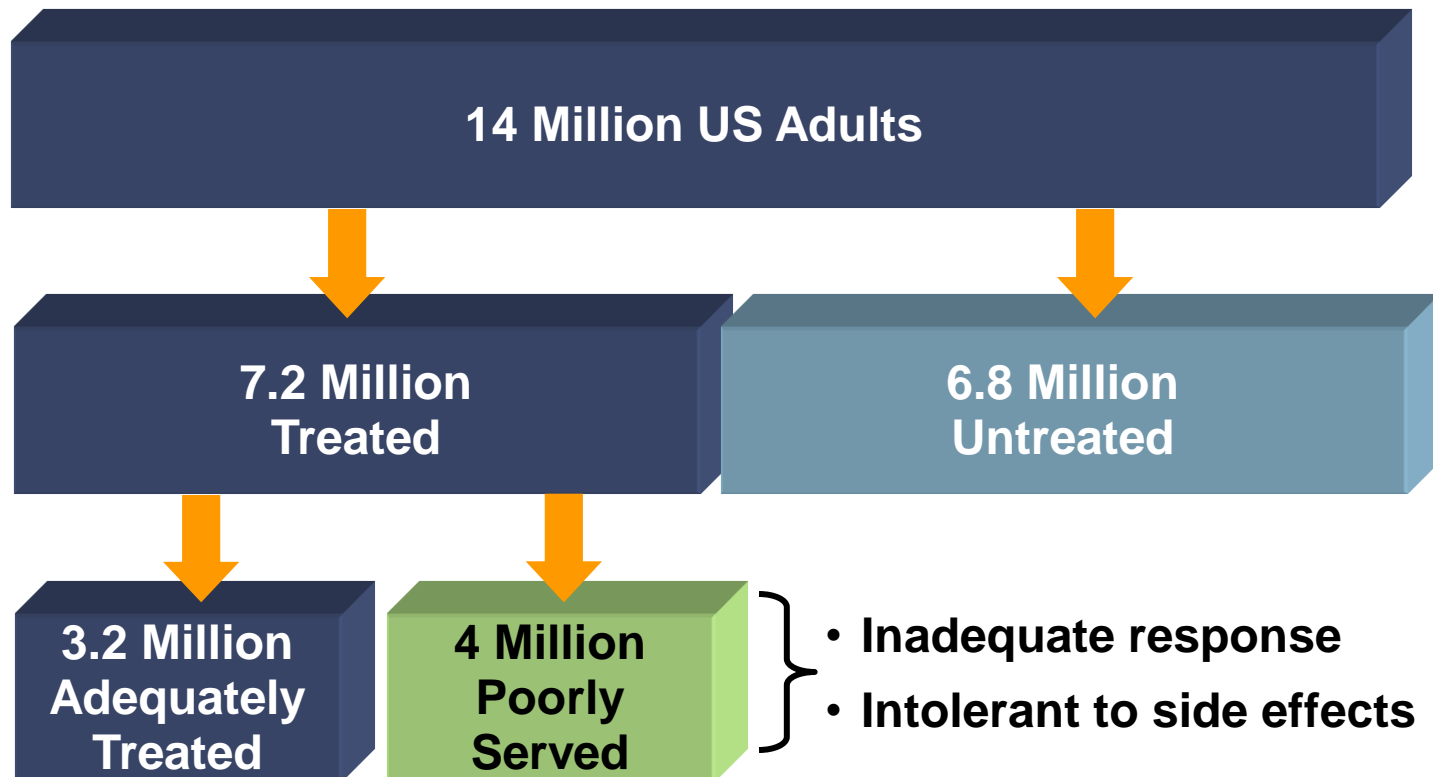
- **Major Depressive Disorder (MDD): When is Additional Help Needed?**
- **What is NeuroStar TMS Therapy?**
- **What is the Evidence for NeuroStar TMS Therapy?**
- **When is NeuroStar TMS Therapy the Right Choice?**



What are the Questions?

- **Major Depressive Disorder (MDD): When is Additional Help Needed?**
 - Epidemiology of MDD
 - Current treatment options
- What is NeuroStar TMS Therapy?
- What is the Evidence for NeuroStar TMS Therapy?
- When is NeuroStar TMS Therapy the Right Choice?

A Significant Percentage of Patients With MDD Remain Poorly Served

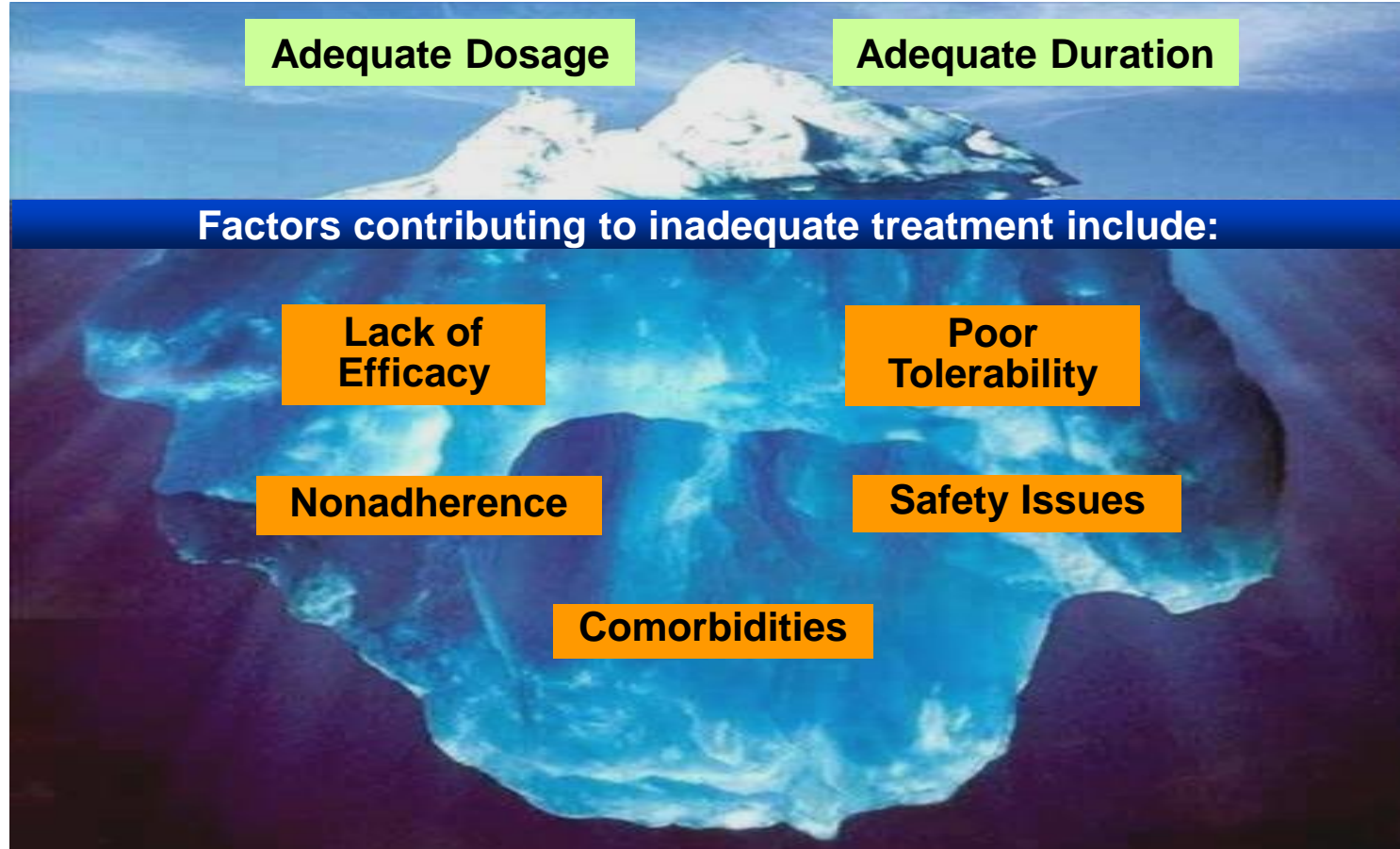


Major Depression

Current Treatment Reality

- **Significant unmet needs exist**
 - Partial or non-response to 1st treatment is common
 - Likelihood of benefit diminishes with each successive treatment failure
 - Some patients remain refractory to all treatments
- ***Adverse events and treatment compliance are significant issues that hinder definitive treatment***

In MDD, “Adequate” Treatment Is Difficult to Achieve¹⁻³



1. Nemeroff CB. *Depress Anxiety*. 1996/1997;4(4):169-181; 2. Oquendo MA et al. *J Clin Psychiatry*. 2003;64(7):825-833; 3. Oquendo MA et al. *Am J Psychiatry*. 1999;156(2):190-194.

Health Service Impact of Incomplete Response to MDD Treatment

- **Significantly more inpatient hospitalizations, outpatient office visits, and psychotropic medications.^{1,2,3}**
- **Average annual costs ranged from between 2 times greater ¹ and 6 times greater ³ compared to treatment-responsive patients**
- **Costs >\$42K versus only \$6.5K for treatment-responsive patients ³**
- **Significantly greater work loss costs (disability and absenteeism) than treatment-responsive patients ¹**
- **Increased direct costs of non-remitters include increased medical utilization for non-psychiatric conditions^{1,2}**

MDD affects other health conditions

- **MDD has been shown to be an independent factor affecting the morbidity and mortality for the following:**
 - **All cause mortality¹**
 - **Acute stroke²**
 - **Diabetes³**
 - **Myocardial infarction⁴**
 - **Cardiovascular disease⁵**
 - **Congestive heart failure⁶**
 - **HIV⁷**

1. Murphy, JM, et al *Arch Gen Psychiatry*. 1987. 44(5)473-480; 2. Everson, SA, et. al. *Arch Intern Med*. 1998; 158(10): 1133-1138; 3. Lustman, PT, et.al. *Diabetes Care*. 2000: 23(7): 934-942; 4. Frasure-Smith, N, et. al. *JAMA*. 1993; 270(15): 1819-1825; 5. Penninx, BW, et. al. *Arch Gen Psych*. 2001; 58(3): 221-227. 6. Vaccarino, V, et. al *J. Am Coll Cardiol*. 2001; 38(1): 199-205. 7. Ickovics, JR, et. *JAMA*. 2001: 285(11): 1466-1474.

Current Treatment Options for Patients with Difficult to Treat Major Depression

Antipsychotic Augmentation

Several atypical antipsychotic agents are FDA-approved as augmentation for partial or non-response to primary antidepressant treatment:

- **Common adverse events:**

- Akathisia
- Headache
- Restlessness

- **Potential serious risks:**

- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Dyslipidemia
- Hyperglycemia

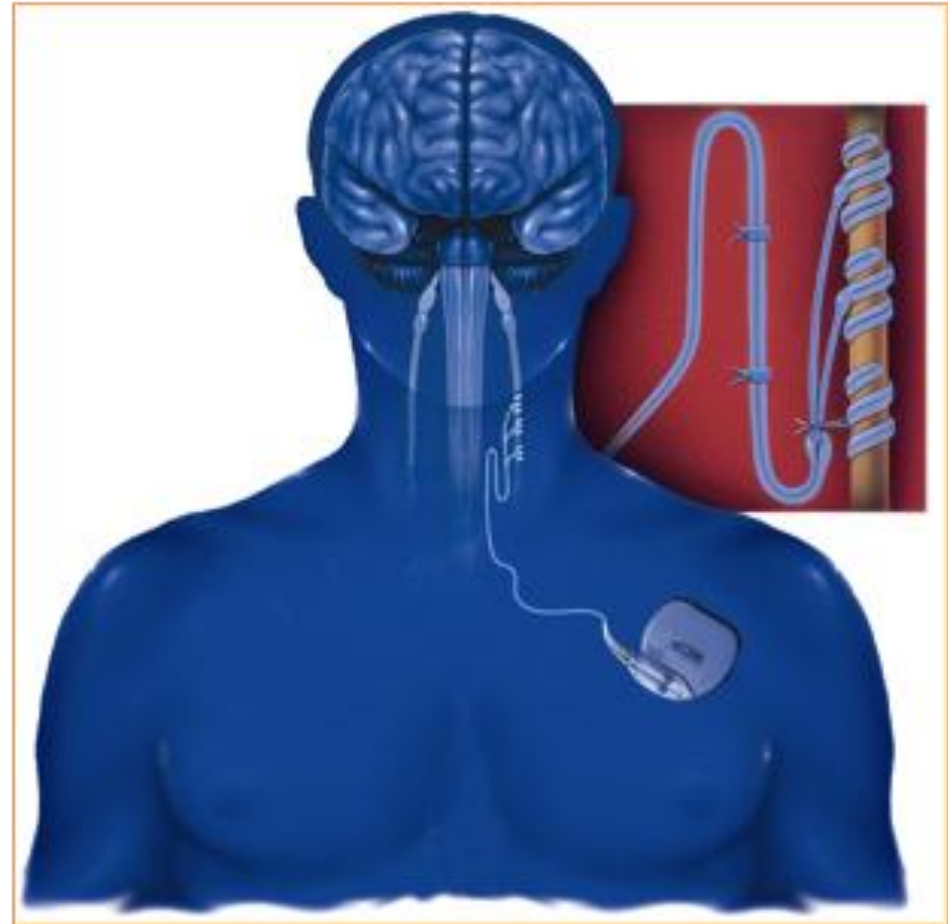
- **Rarely: Coma, Death**

Electroconvulsive Therapy (ECT)

- **Oldest of the contemporary antidepressants (first published use 1938)**
- **FDA status: No RCT data for acute efficacy since mid-80's**
- Considered to be an effective acute antidepressant,
 - Primary use in immediate life-threatening clinical settings
- Despite modern technical advances,
 - Risk of muscle paralysis and anesthesia remains,
 - Persistent cognitive deficits occur in a small percent of patients

Vagus Nerve Stimulation (VNS)

- **First approved for use in medication-refractory partial seizures**
- **Approved for use as adjunct in severely resistant major depression**
- *Invasive antidepressant treatment*
- *Adverse events: surgical risks, voice alteration, limited MRI exclusion*



Unmet Needs: Summary

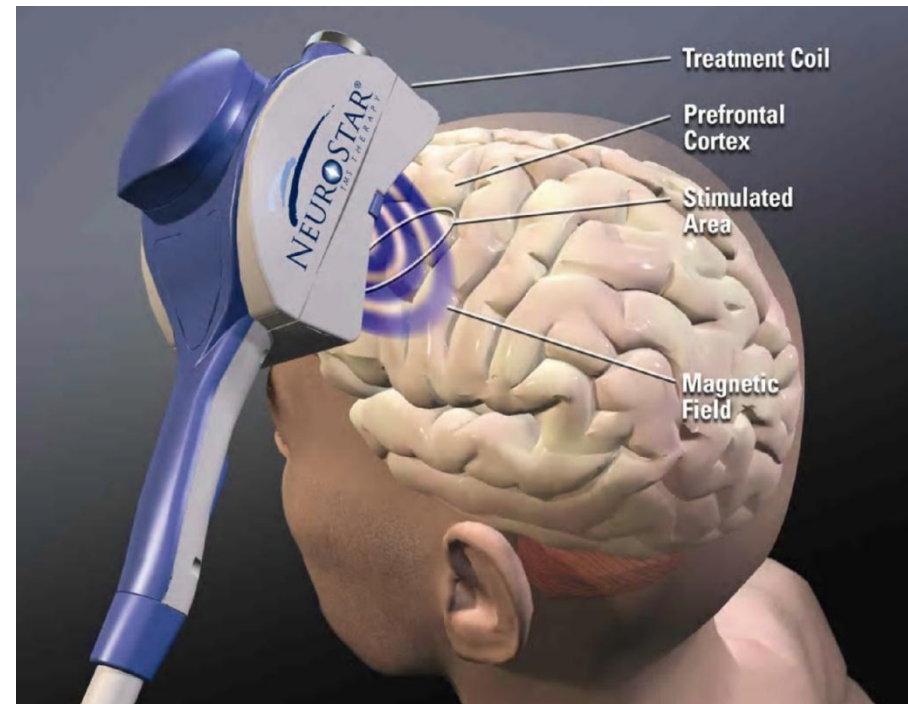
- **Of the 14 million adults in the US with MDD, only half seek treatment**
 - **Of these, 4 million remain poorly served**
- **Poor tolerability is a major cause of treatment discontinuation**
- **MDD has a significant negative impact in health economic terms and on general health status**
- **There are few FDA-approved treatment options specifically studied in treatment resistant patients**
- **There remains an unmet need for novel treatment options that address these issues**

What are the Questions?

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- **What is NeuroStar TMS Therapy?**
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Transcranial Magnetic Stimulation (TMS)

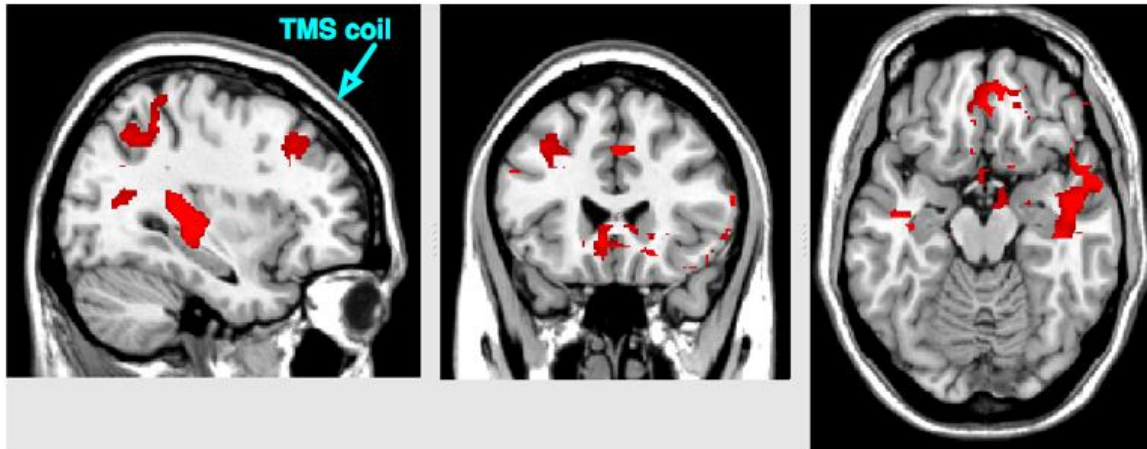
- **Application of electromagnetic induction described by Michael Faraday in 1839**
 - **Faraday's Law: a time-varying magnetic field induces an electric current that runs perpendicular to the time-varying motion of the magnetic field^{1,2}**
- **Clinical application: Pulsed magnetic fields can induce electrical currents in brain tissues and neurons³**



Biological Effects of TMS

Acute Effects

- Induces electric current
- Depolarizes neurons in superficial cortex
- Leads to local and trans-synaptic changes in brain activity



Example:

Left prefrontal TMS

23 depressed individuals

**Activation demonstrated
at site of stimulation and
also at synaptically
connected cortical and
subcortical regions**

TMS Therapy in Clinical Practice

- **Noninvasive, non-systemic**
- **Effective and well-tolerated**
- **No anesthesia or sedation**
- **Outpatient procedure easily performed in psychiatrists' offices**
- **Approximately 37 minute procedure**
- **Observed therapy**



NeuroStar TMS Therapy

A New Treatment for Major Depression

- **NeuroStar is the *only* TMS system FDA cleared for the treatment of major depressive disorder**
 - ***No other TMS device has established safety or efficacy in the treatment of major depression***
- **NeuroStar TMS system is *designed* and *proven* to deliver safe and effective treatment for depression in the clinical setting**

NeuroStar TMS Therapy

Design Innovations for Safe and Effective Clinical Use

System Features:

- **User-assisted software in setting treatment level**
- **Guides user to proper targeting placement of coil for treatment (laser-assisted)**
- **Embedded controls guides system operation within standard safe performance limits**

NeuroStar TMS Therapy

Design Innovations for Safe and Effective Clinical Use

SenStar Treatment Link:

This patient interface links with the NeuroStar TMS system to provide consistent magnetic field intensity and correct coil placement.

- **Built-in detector ensures correct magnetic field exposure**
- **Maximizes patient contact for consistent stimulation of the targeted tissue**
- **Reduces stimulation of the scalp to enhance patient comfort**



NeuroStar TMS Therapy Demonstration Video

(3 minutes)

Insert Video Here

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NeuroStar TMS Therapy: Acute Efficacy in Indicated Population From Randomized Controlled Trial (RCT)

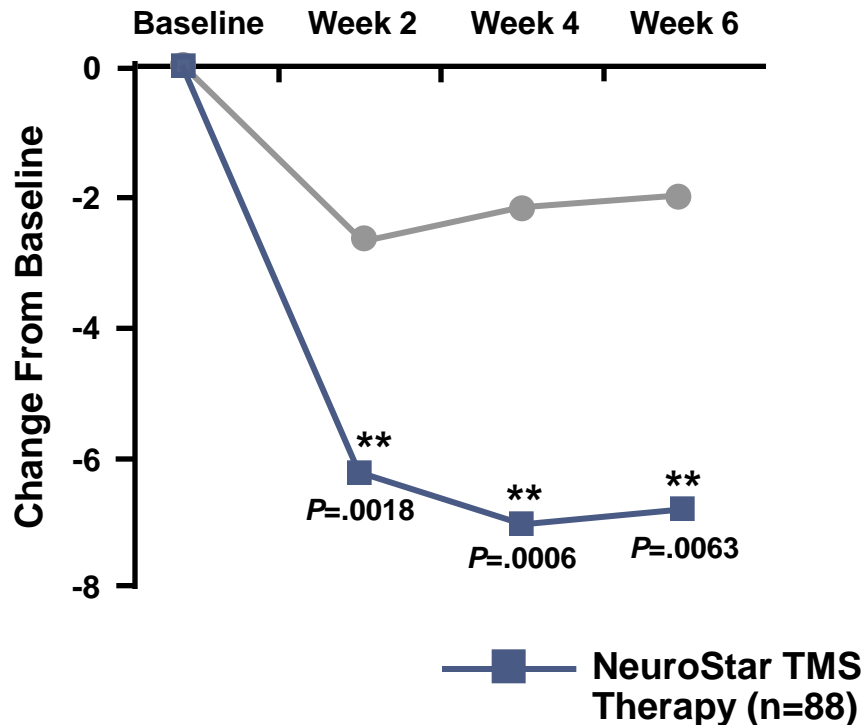
Who Was Studied?

- **Diagnosis, Disease Severity & Illness Course**
 - DSM-IV Diagnosis: Major Depressive Disorder, unipolar, non-psychotic
 - Average age ~50 years
 - Largely (~95%) recurrent illness course
 - Approximately 50% unemployed due to illness
 - Moderate to severe symptom burden
 - Avg. HAMD24 ~30, MADRS ~32 at study entry
- **Antidepressant Treatment History**
 - Moderate to severe treatment resistance in current episode
 - *Nearly all received multiple ineffective treatments in current episode (range: 1 to 23 attempts, avg.: 4)*

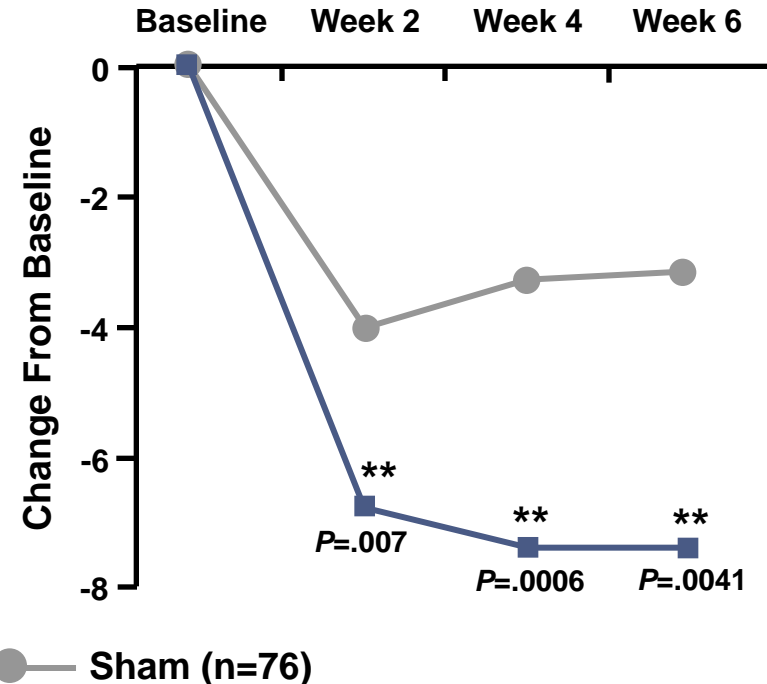
NeuroStar TMS Therapy Produced Significant Improvements in Depressive Symptoms

Indicated Population

**MADRS Total Score
(Baseline to Endpoint Change)**



**HAMD-24 Total Score
(Baseline to Endpoint Change)**



** $P < .01$.

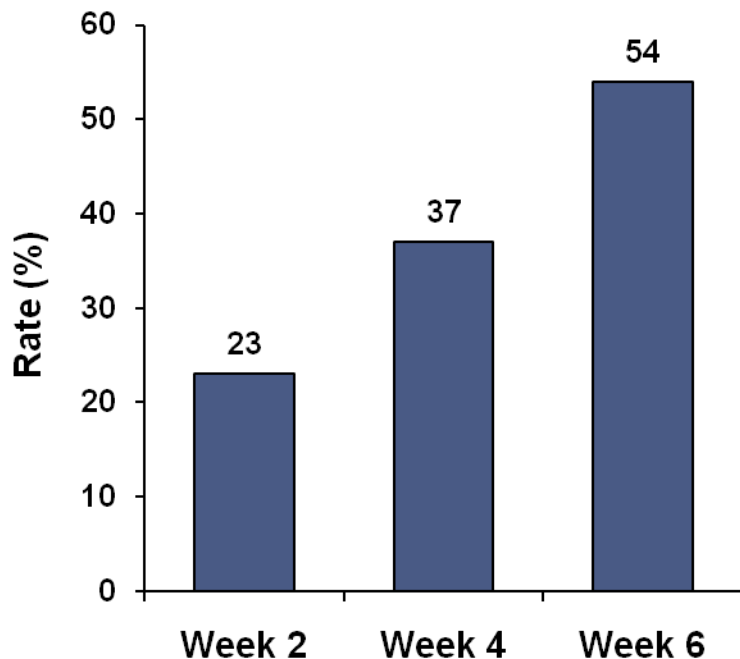
LOCF analysis of evaluable study population.

Demitrack, MA, Thase, ME, *Psychopharm Bulletin*. 2009, (42(2): 5-38

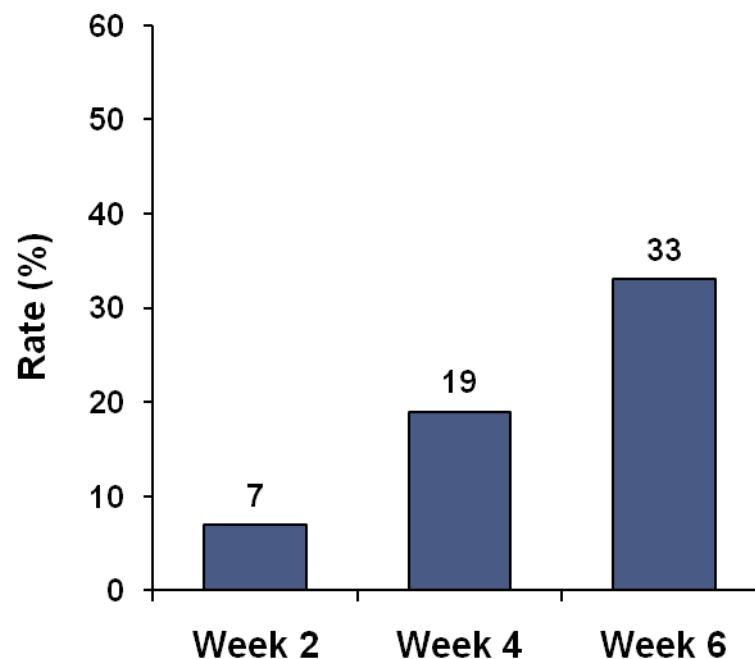
NeuroStar TMS Therapy: Acute Efficacy in Indicated Population During Open-Label Treatment

NeuroStar TMS Therapy: Clinically Meaningful Response and Remission Rates in Indicated Population

HAMD-24 Response Rates
(>50% Improvement from Baseline)



HAMD-24 Remission Rates
(HAMD-24 Total Score <11)



Sham treatment to Active treatment (**N=43**)

Safety and Tolerability of NeuroStar TMS Therapy

NeuroStar TMS Therapy: Safety Overview

- **No systemic side effects such as weight gain, sexual dysfunction, nausea, dry mouth, or sedation**
- **No adverse effect on cognition**
- **Most common adverse events were headache and scalp discomfort during active treatment**
 - **< 5% of patients discontinued due to adverse events**
- **No seizures during clinical studies (over 10,000 treatments)**
 - ***One seizure reported in post-marketing period (~20,000 treatment sessions completed in post-marketing experience to date)***

Contraindications and Warnings

- **NeuroStar® TMS Therapy is contraindicated in patients with implanted metallic devices or non-removable metallic objects in or around the head.**
- **The NeuroStar TMS System should be used with caution in patients who have an implanted device that is activated or controlled by physiologic signals such as pacemakers or implantable cardioverter defibrillators (ICDs) because the TMS magnetic field could affect their functioning.**
- **Refer to [Neurostartms.com](https://www.neurostartms.com) for additional product safety information**

NeuroStar TMS Therapy

Summary of Clinical Evidence

- ***Efficacy established in largest multi-site, randomized, sham-controlled TMS clinical trial conducted to date:***
 - ***Primary outcome (MADRS): 22.1% reduction in MADRS total score with active NeuroStar TMS vs 9.1% on sham***
 - ***Clinically meaningful effect size = 0.52***
- ***In open label extension study, 1 in 2 patients reached response, 1 in 3 patients achieved remission***
- ***In a 6 month, open-label follow up study that allowed TMS reintroduction if needed, <10% of patients experienced relapse of illness***
- ***Safety and tolerability shown to be excellent***

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NeuroStar TMS Therapy

Indication for Use

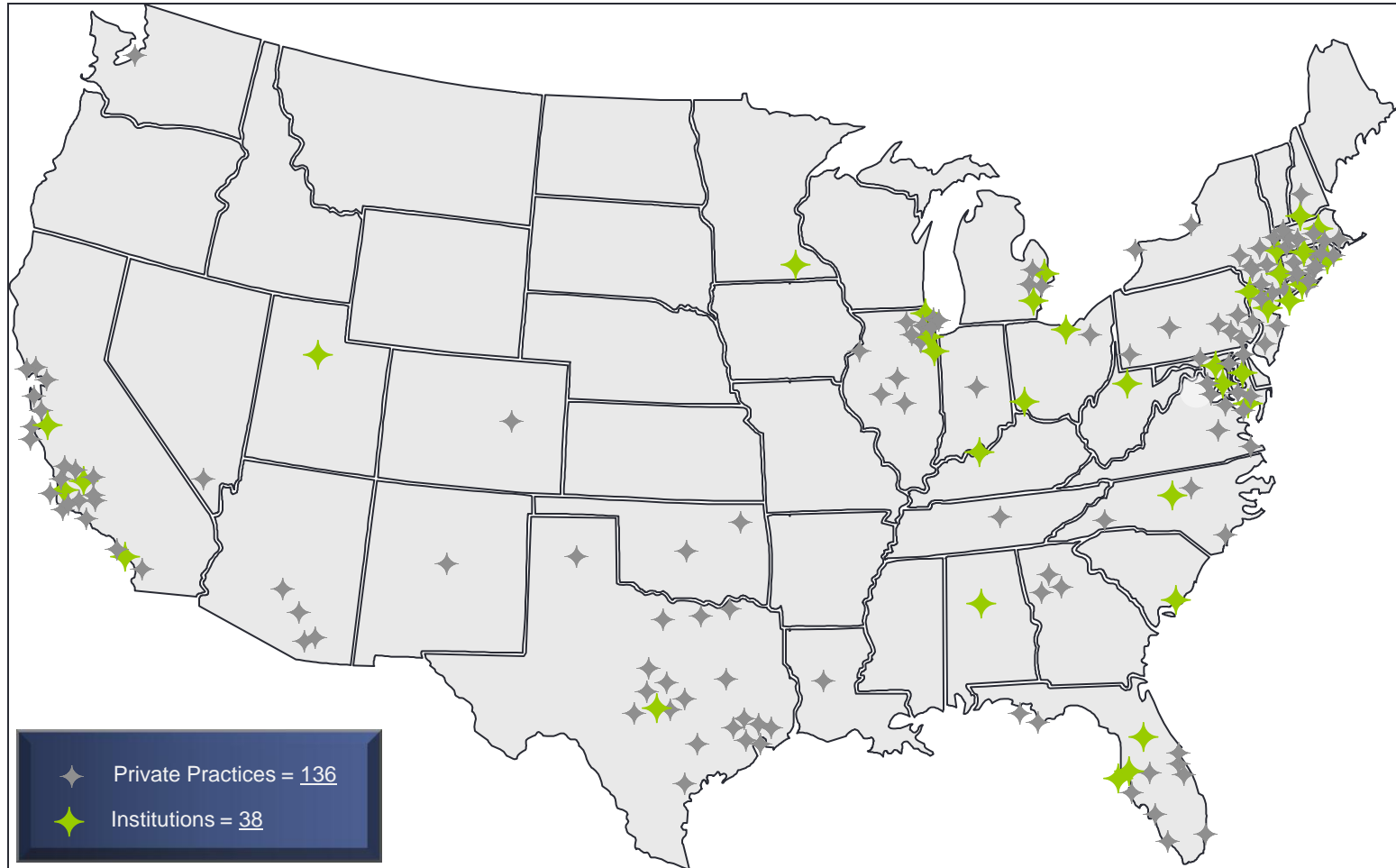
“The NeuroStar TMS System is indicated for the treatment of adult patients with Major Depressive Disorder (MDD) who have failed to receive satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode...”

Nearly all patients received multiple ineffective treatments in current episode (range: 1 to 23 attempts, avg: 4)

NeuroStar TMS Therapy Use in Real World Practice

NeuroStar Practice Locations

More than 20,000 TMS Sessions Administered



Updated: March, 2010

Key Academic Medical Centers Offering NeuroStar TMS Therapy



1. **Massachusetts General Hospital, Boston**
2. **Johns Hopkins Hospital, Baltimore**
3. **McLean Hospital, Belmont, Mass.**
4. **New York-Presbyterian University Hospital of Columbia and Cornell**
5. **UCLA's Neuropsychiatric Hospital, Los Angeles**
6. **Sheppard and Enoch Pratt Hospital, Baltimore**
7. **Mayo Clinic, Rochester, Minn.**

Other notable institutions include: U of Michigan, Butler Hosp./Brown Univ., Medical Univ. of S. Carolina, Rush, BIDMC/Harvard, U of Cincinnati/LCOH, Walter Reed, U of Florida, Loma Linda University, Boston Univ., U of S. Florida, and S. Illinois Univ.

NeuroStar Treatment Utilization Study

Demographics

- **57% Females**
- **Avg age = 49.9 yrs (median = 51.0 yrs)**

Primary Diagnosis

- **82% with moderate to severe unipolar, non-psychotic Major Depressive Disorder**

Antidepressant Treatment History

- **Avg # of psychiatric meds in current episode = 3.4**
- **Majority of patients using complex combination antidepressant medications**

Quality of Life and Economic Benefits

- **NeuroStar TMS shows improvements in standard measures of functional status and quality of life**
- **When NeuroStar TMS is compared to current standard of care using complex combination antidepressant medications,**
 - **TMS results in decreased # days lost due to illness, and increased work productivity,**
 - **TMS results in a net cost savings relative to current pharmaceutical standard of care**

Simpson, KN, Welch, MJ, Kozel, FA, et al. Adv in Therapy 2009; 29(3):346-368; Neuronetics, Inc, data on file.

NeuroStar TMS Therapy

What Are the Answers?

Major Depressive Disorder (MDD): When is Additional Help Needed?

- *When more medications don't help*

What is NeuroStar TMS Therapy?

- *NeuroStar TMS is a non-invasive, non-systemic treatment for major depression*

What is the Evidence for NeuroStar TMS Therapy?

- *NeuroStar TMS is a cost-effective, safe and well-tolerated treatment for major depression*

When is NeuroStar TMS Therapy the Right Choice?

- *NeuroStar TMS is a compelling choice when initial treatments have failed*

For Complete Safety and Efficacy Data and Additional Information:

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