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# 11TH ANNUAL **CHAIR SUMMIT**

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Master Class for Neuroscience Professional Development

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# **Promoting Change in the Management of Treatment-Resistant Depression: Neuromodulation in Remission and Recovery**

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# Learning Objective 1

Evaluate the clinical efficacy and safety of invasive (e.g., DBS, VNS) and non-invasive (e.g., ECT, TMS) neuromodulation techniques as an alternative (or adjunctive) therapy to manage treatment-resistant depression.



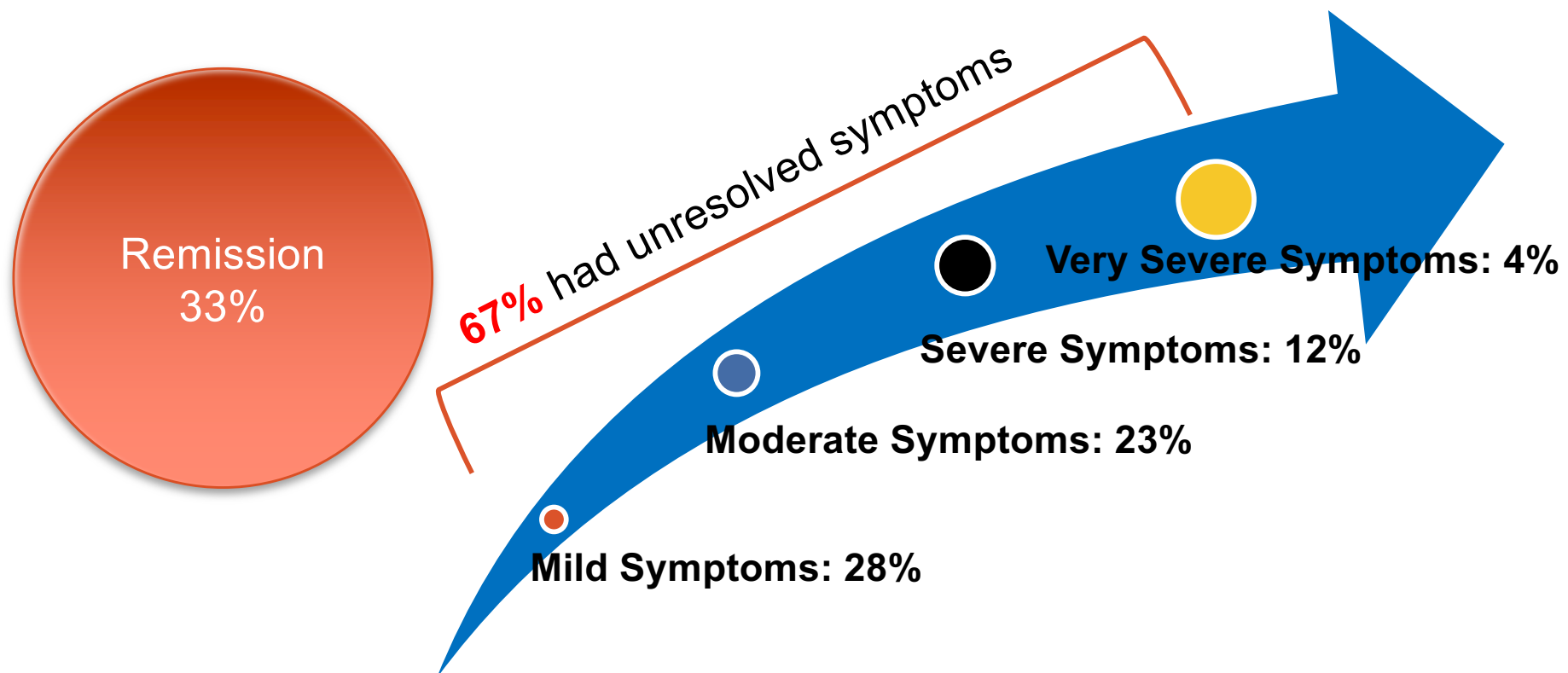
# Sequenced Treatment Alternatives to Relieve Depression (STAR\*D)



- An effectiveness study; N = 2,876
- Step 1 citalopram: remission rate 37%
- Step 2 a different selective serotonin reuptake inhibitor (SSRI): remission rate 31% of the remainder
- Step 3 includes cognitive behavioral therapy: 14%
- Step 4: 13%



# STAR\*D: Unresolved Symptoms Following Antidepressant Treatment



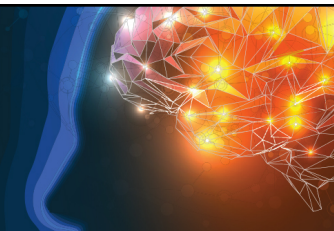
Trivedi M, et al. *Am J Psychiatry*. 2006;163:28-40.

# Keeping Track of Treatment Progress (To Recognize Failure or Success) “Measurement-Based Care”



- Strongly recommend a short self-rating scale
  - Beck Depression Inventory (versions I and II)
  - Patient Health Questionnaire (PHQ-9)
- Apart from looking at the global score, it allows you to zoom in on problem areas and monitor suicidality

# Staged Treatment-Resistant Depression (TRD)



- Stage 0: Patient not treated
- Stage 1: Failure to respond to 1 adequate antidepressant medication trial
- **Stage 2: Failing 2 adequate antidepressant trials**
- Stage 3: Stage 2, plus failure after an augmentation
- Stage 4: Failure of a second augmentation strategy
- Stage 5: Failure to respond to electroconvulsive therapy (ECT)

# Why Don't More Depressed Patients Get Well?



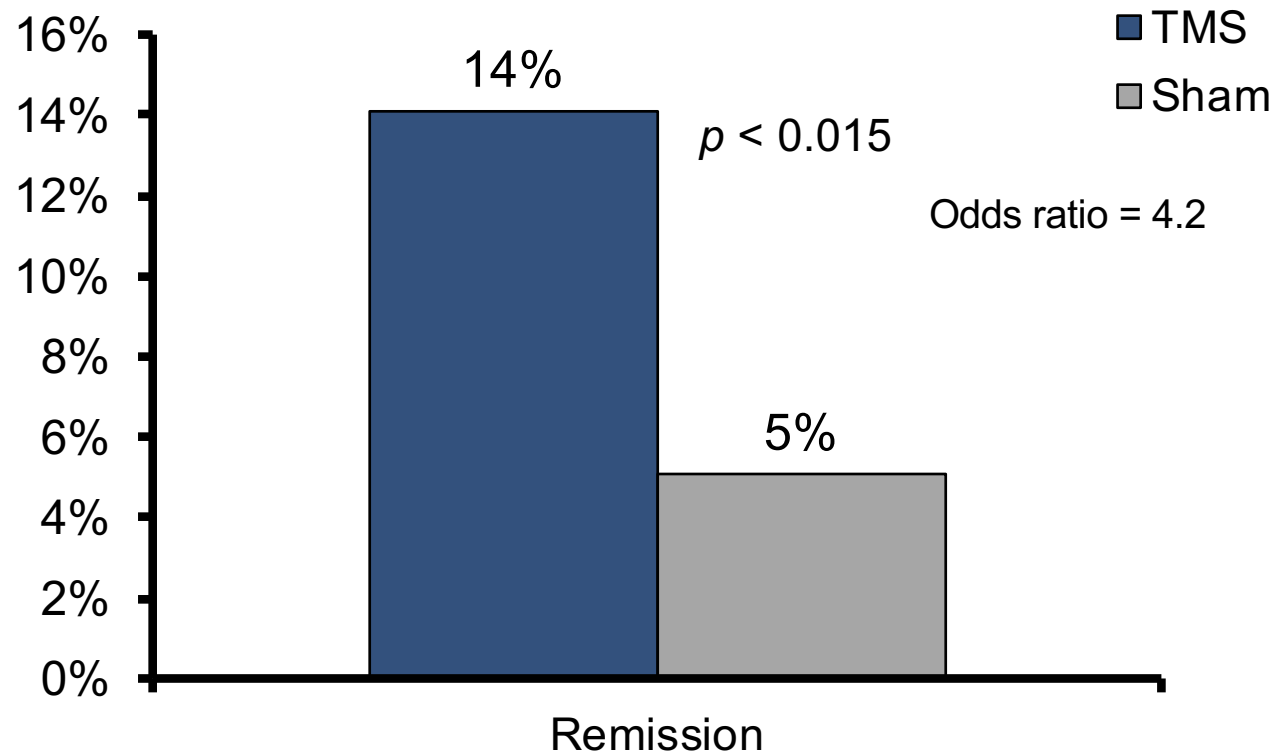
- Major depressive disorder (MDD) is a heterogeneous disorder (i.e., we don't know what we are diagnosing, where it comes from, what we are treating)
- It is among the DSM-5 diagnoses with the worst inter-rater reliability
- It may actually be a set of different conditions, some of which respond to SSRIs and some do not
- It may be confused with other disorders—wrong diagnosis!—“pseudo-resistance”



# NIMH Multi-Site Study OPT-TMS with an Active Sham Control (n = 190)



Patients were free of antidepressants for 2 wks before baseline assessment (5 wks for fluoxetine) and for the duration of active treatment.



NIMH = National Institute of Mental Health. (Baseline HAMD =26; Remission: HAMD score <4)

George MS, et al. *Arch Gen Psychiatry*. 2010;67:507-516.

# TMS FDA-Approved Indication



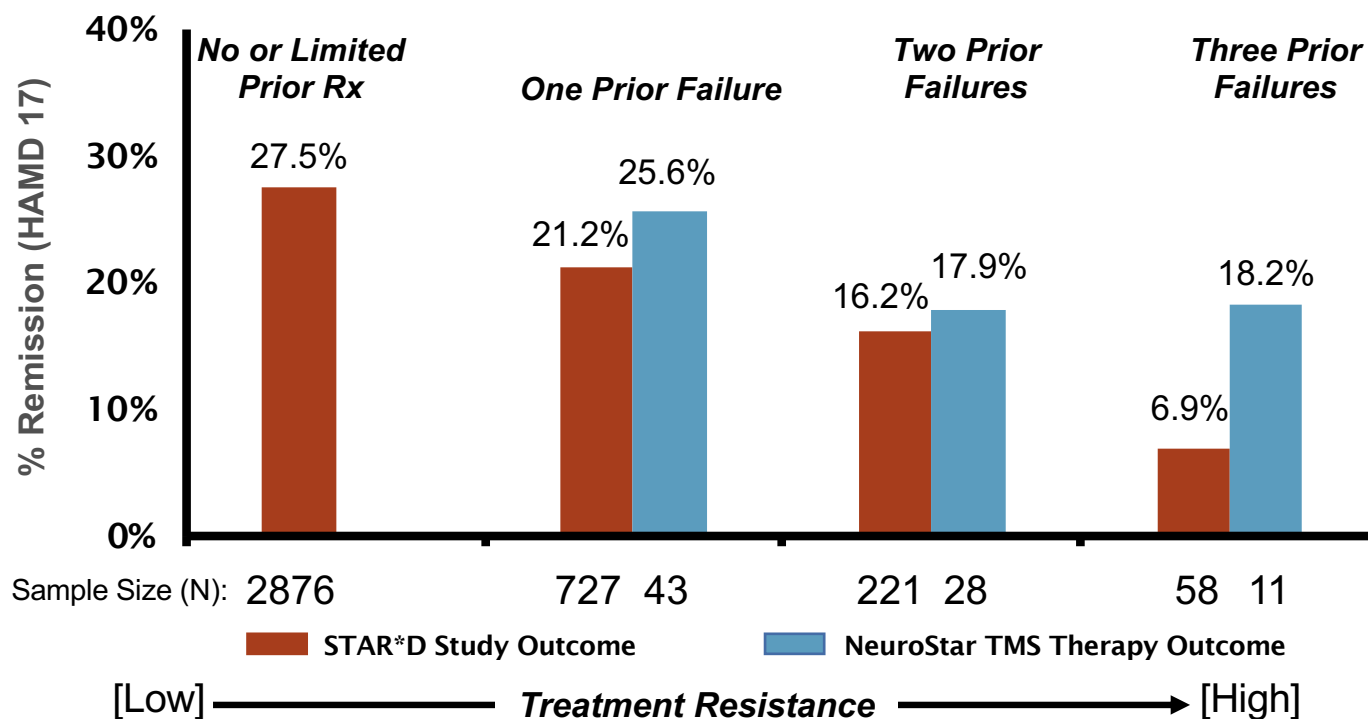
“FDA has determined that the NeuroStar TMS System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.”

510(k) approval (clearance), 2008

FDA = Food and Drug Administration.

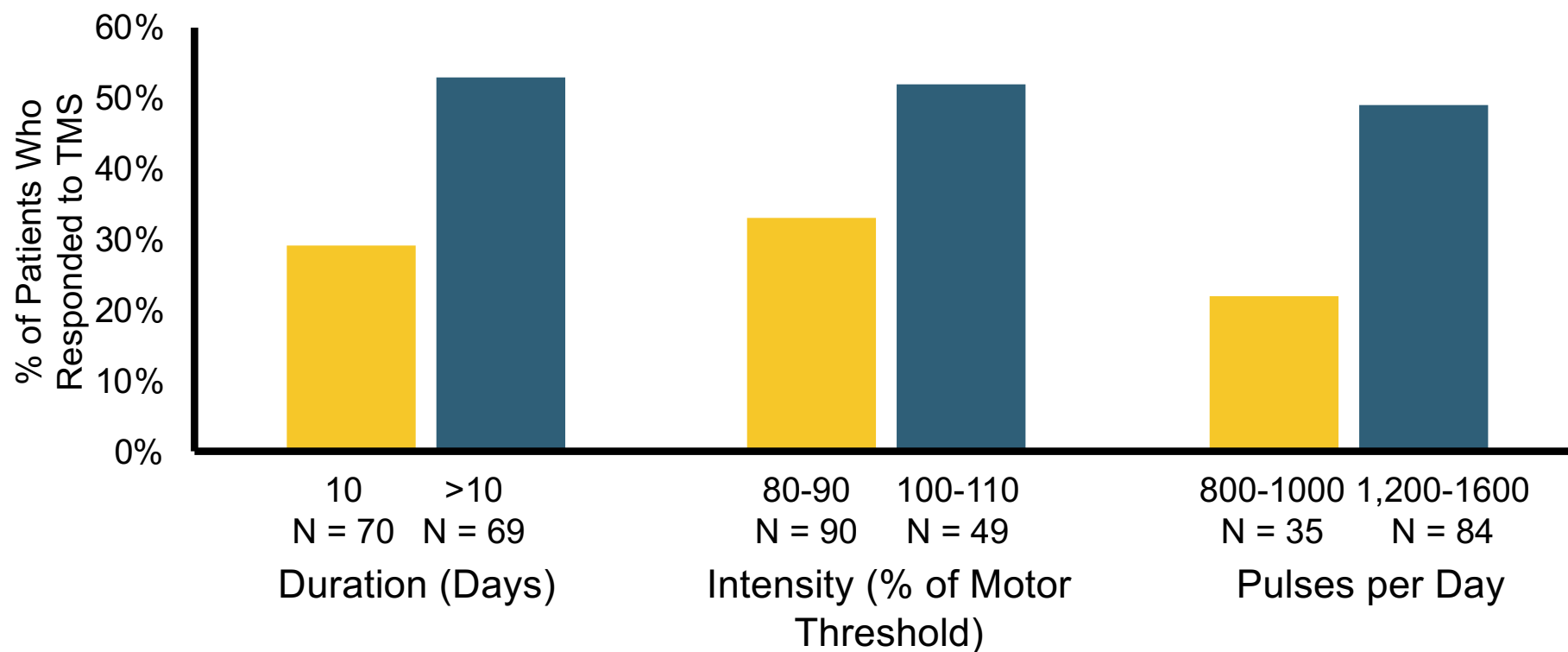
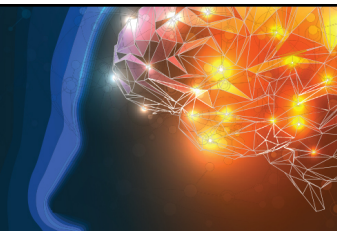
# Clinical Benefit Varies by Prior Treatment Failure in STAR\*D and NeuroStar TMS Therapy (Study 102)

## Comparison of Monotherapy Outcomes: Pharmacotherapy Versus NeuroStar TMS Therapy



Thase ME, et al. *Biol Psych*. 2008;63(7):Suppl:138s. (TMS patients were medication-free)

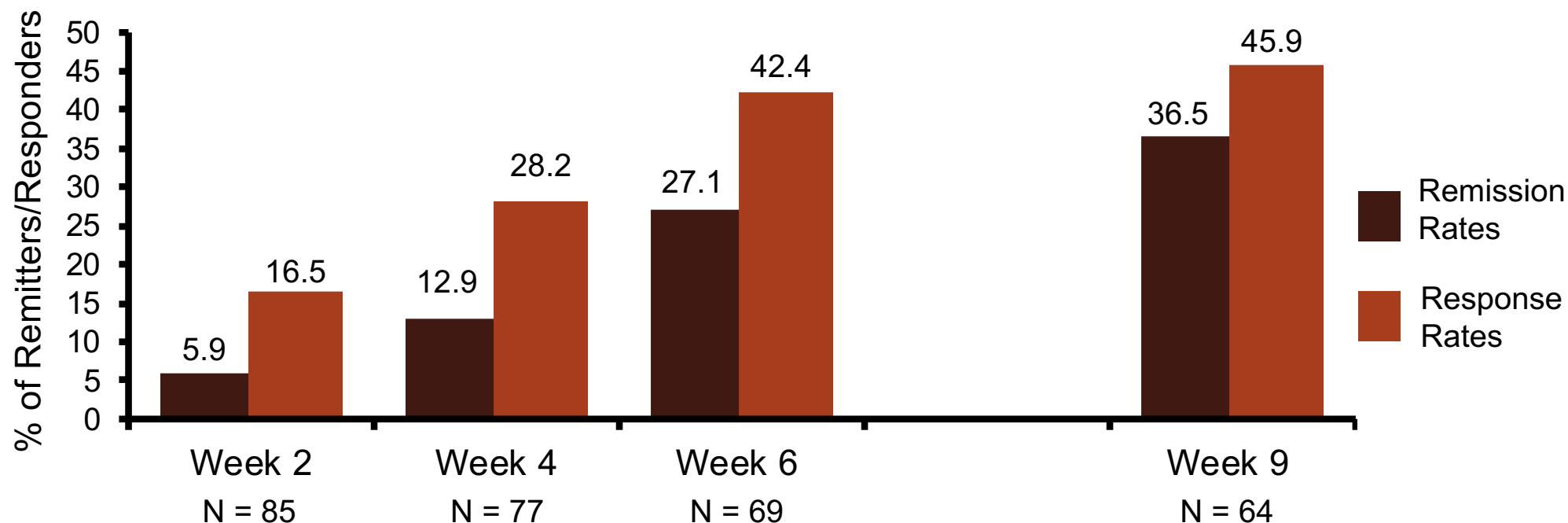
# TMS Dose-Response Findings



Gershon AA, et al. *Am J Psychiatry*. 2003;160:835-845.



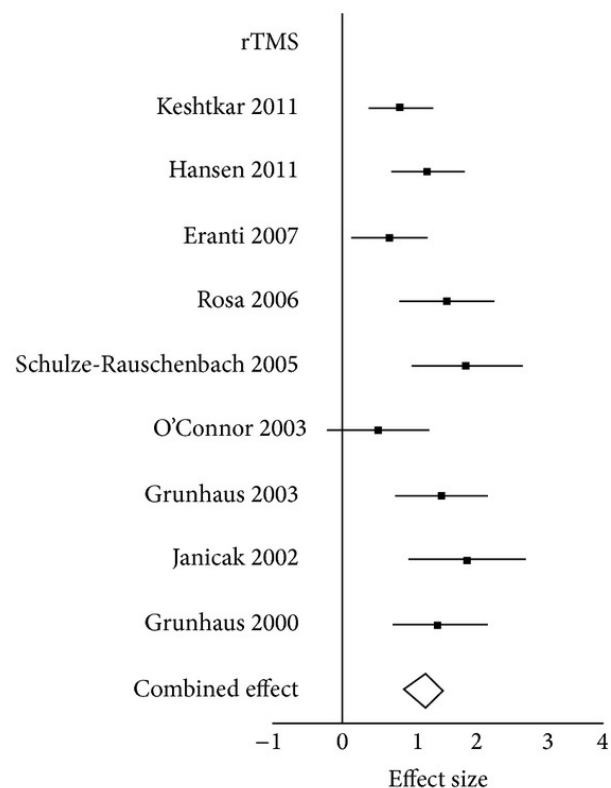
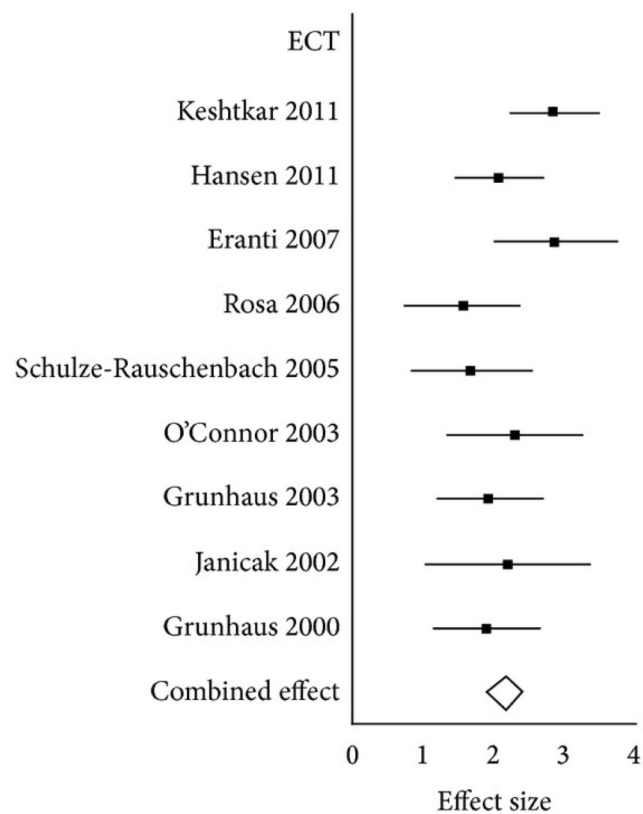
# Extension Trial of Patients Who Have Failed 6 Wks RCT of TMS v Sham: Open-Label Acute TMS, Followed by TMS Taper and Introduction of Antidepressants



Remission is MADRS < 10

Avery DH, et al. *J Clin Psychiatry*. 2008;69:441-451.

# ECT and rTMS Effect Sizes in Depressed Patients



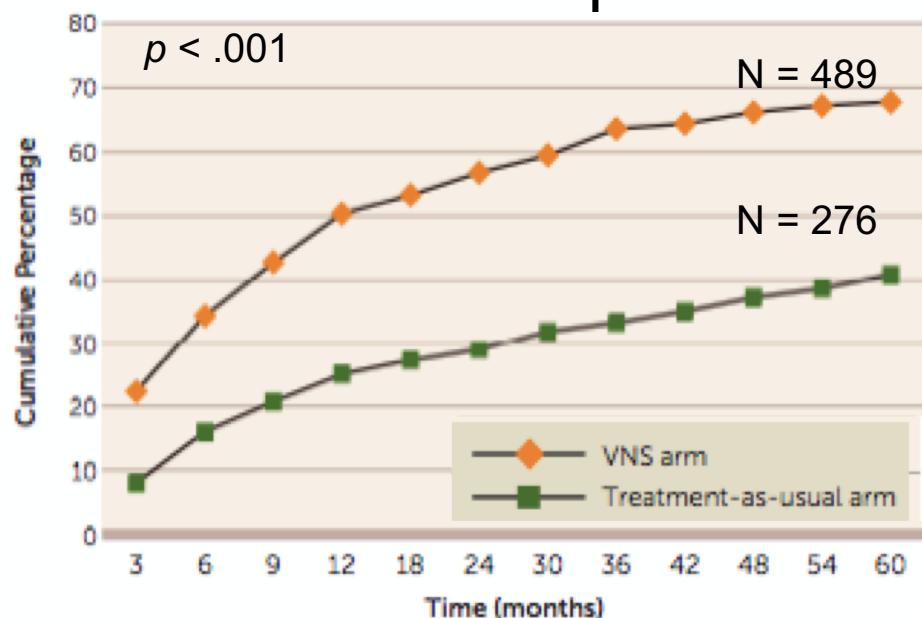
rTMS = repetitive TMS.

Micallef-Trigona B. *Depress Res Treat.* 2014;2014:135049.

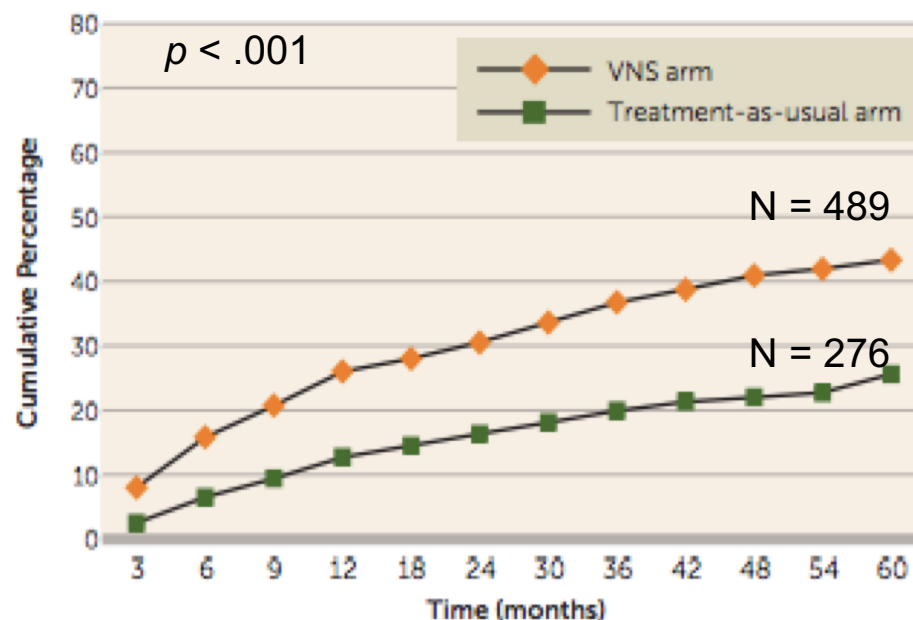
# 5-Year Open-Label Study of Response and Remission Rates in TRD With and Without Vagus Nerve Stimulation (VNS)



## First-Time Response



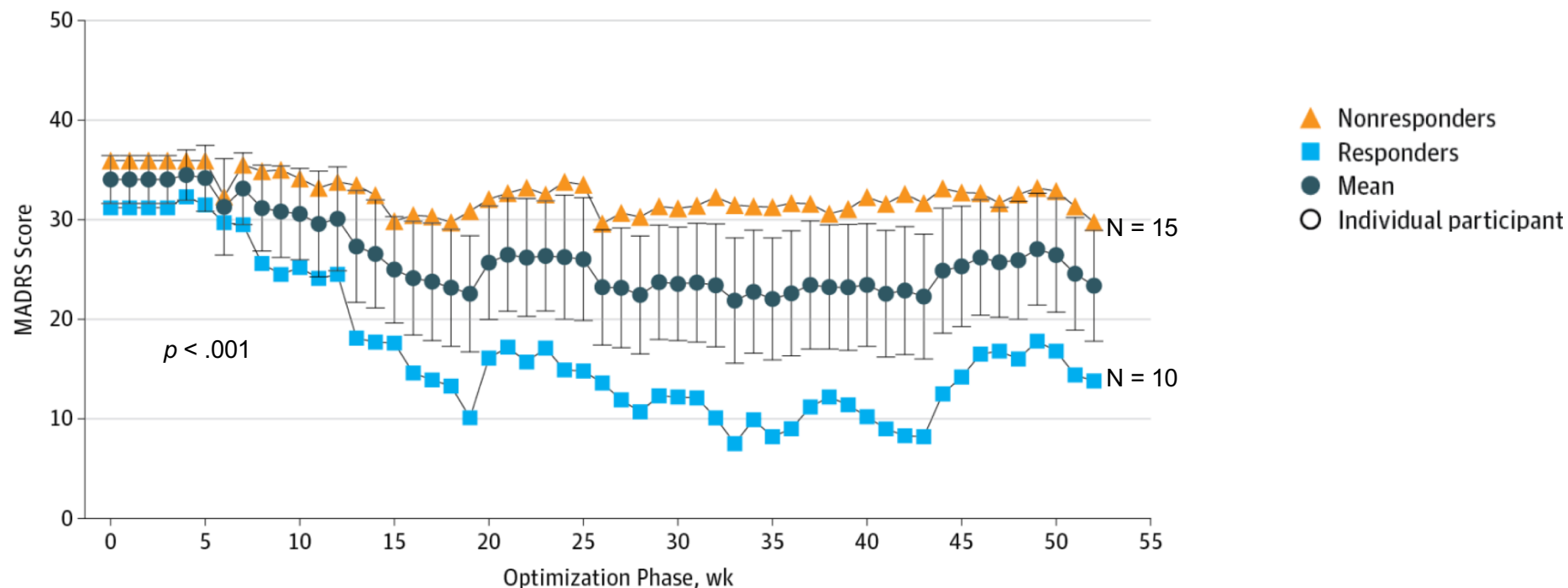
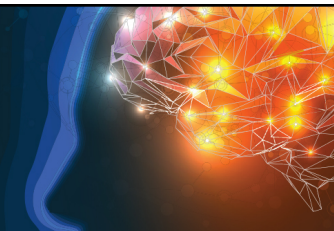
## First-Time Remission



Response defined as an improvement of  $\geq 50\%$  from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score.  
Remission defined as a decrease to a score of 9 on the MADRS at any postbaseline visit.

Aaronson ST, et al. *Am J Psychiatry*. 2017;174:640-648

# Open-Label Bilateral DBS\* in Internal Capsule in Patients with TRD (N = 25)



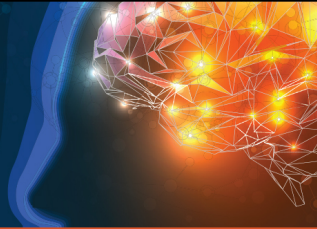
\*DBS (Deep Brain Stimulation) is FDA-approved for treatment-resistant OCD under Humanitarian Device Exemption (HDE). It is currently experimental for TRD.

Bergfeld IO, et al. *JAMA Psychiatry*. 2016;73(5):456-464.



# SMART Goals

**Specific, Measurable, Attainable, Relevant, Timely**



- Identify patients with treatment-resistance who are suitable for neuromodulation strategies
- Educate patients about neuromodulation strategies and what to expect from each treatment approach

# Questions & Answers

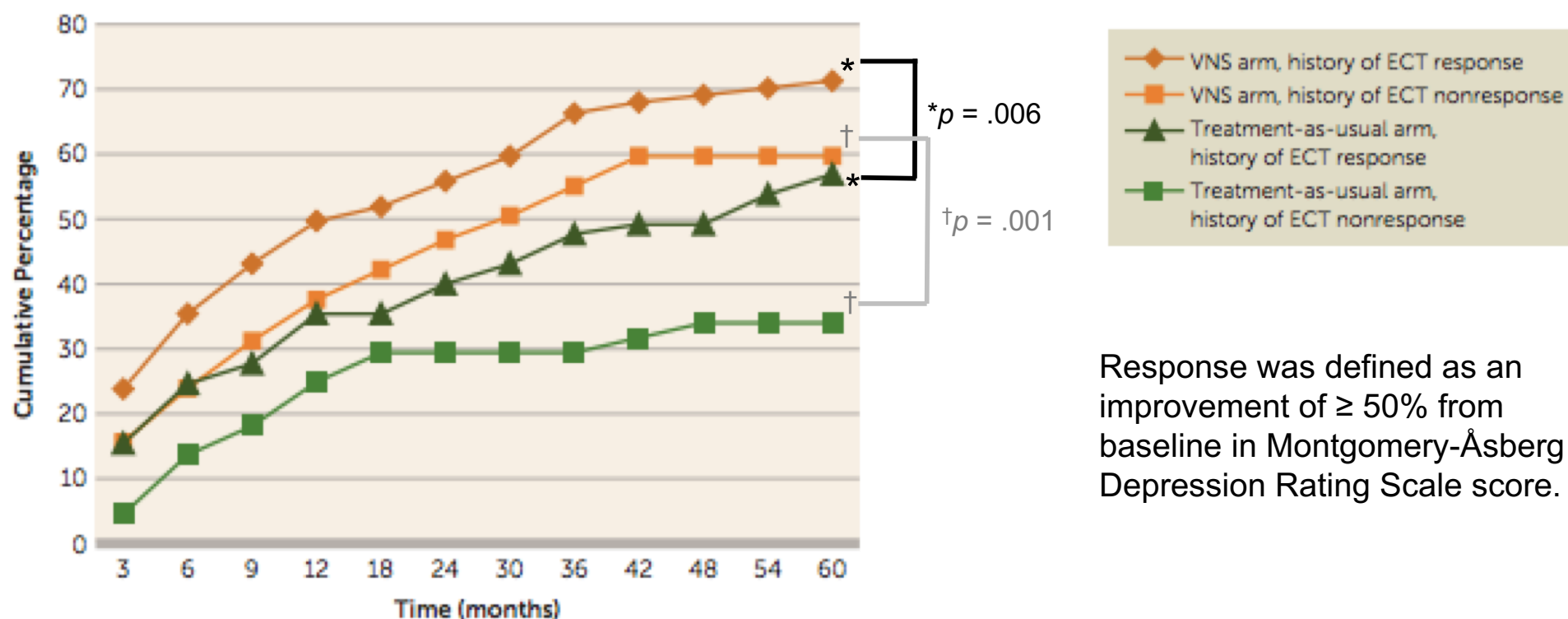
Don't forget to fill out your evaluations to collect your credit.



# Resources



# First-Time Response in TRD with/without VNS and History of Response/Nonresponse to ECT



Response was defined as an improvement of  $\geq 50\%$  from baseline in Montgomery-Åsberg Depression Rating Scale score.



# Impact of Bilateral DBS\* in Internal Capsule in TRD (N = 25)



Table 2. Mean Depression Scores Over Time

Characteristic	Optimization Phase										Crossover Phase			
	Baseline		T1		T2 <sup>a</sup>		T3		T4		Sham		Active	
	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)
All														
HAM-D-17	25	22.2 (4.9)	25	21.9 (6.2)	25	15.9 (9.2)	16	16.0 (7.8)	16	20.7 (7.8)	16	23.1 (5.1) <sup>b</sup>	16	13.6 <sup>b</sup> (7.8) <sup>b</sup>
MADRS	25	34.0 (5.8)	25	33.8 (8.5)	25	23.8 (13.7)	16	24.6 (13.1)	16	30.9 (11.6)	16	34.1 <sup>b</sup> (7.7) <sup>c</sup>	16	21.3 (13.5) <sup>c</sup>
IDS-SR	25	49.3 (10.1)	25	48.2 (11.9)	25	38.8 (18.4)	16	36.8 (18.5)	16	42.5 (15.4)	16	46.6 (11.3) <sup>d</sup>	16	32.6 (19.1) <sup>d</sup>
Nonresponder														
HAM-D-17	15	22.6 (4.0)	15	21.9 (3.8)	15	21.5 (7.3)	7	20.1 (5.8)	7	21.9 (5.5)	7	23.0 (4.8)	7	19.0 (5.8)
MADRS	15	35.9 (4.7)	15	35.3 (5.3)	15	32.3 (10.2)	7	32.7 (7.6)	7	35.3 (5.4)	7	35.1 (6.5)	7	32.9 (6.7)
IDS-SR	15	54.5 (6.9)	15	51.1 (9.7)	15	49.2 (14.1)	7	48.7 (13.3)	7	51.1 (10.2)	7	52.0 (11.7)	7	47.9 (11.7)
Responder														
HAM-D-17	10	21.5 (6.1)	10	21.9 (8.8)	10	8.0 (4.7)	9	12.8 (7.9)	9	19.8 (9.5)	9	23.1 (5.6)	9	9.4 (6.6)
MADRS	10	31.2 (6.5)	10	31.5 (11.8)	10	11.8 (7.4)	9	18.2 (13.3)	9	27.4 (14.1)	9	33.3 (8.8)	9	12.3 (9.9)
IDS-SR	10	42.0 (9.4)	10	43.8 (14.0)	10	23.2 (12.0)	9	27.4 (17.0)	9	35.8 (15.8)	9	42.4 (9.5)	9	20.8 (14.9)

Abbreviations: HAM-D-17, 17-item Hamilton Depression Rating Scale; IDS-SR, Inventory of Depressive Symptomatology-Self-report; MADRS, Montgomery-Åsberg Depression Rating Scale; T1, 3 weeks after surgery with stimulation off; T2, following optimization phase; T3 and T4, following first and second crossover blocks, respectively.

<sup>a</sup> Response and nonresponse based on the HAM-D-17 scores at T2.

<sup>b</sup>  $P < .001$ .

<sup>c</sup>  $P = .002$ .

<sup>d</sup>  $P = .001$ .

\*DBS is not FDA-approved for the treatment of TRD.

Bergfeld IO, et al. *JAMA Psychiatry*. 2016;73(5):456-464.