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Evaluating Clinical Significance of Treatment Outcomes in Studies of Resistant Major Depression

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Abstract

Background: The efficacy of antidepressant interventions can be examined in terms of statistical significance, a standardized effect size, or measures of clinical significance. An intervention typically needs to deliver at least a moderate size effect (i.e., Cohen's d >0.4 or >10% difference in response rates) in order to be considered clinically significant. In this presentation, the efficacy of TMS in a large, registration quality study is calibrated against the performance of other relevant strategies for treatment resistant depression.

Methods: Results of the recent TMS trial (i.e., change on the HAMD and MADRS and response and remission rates for the active and sham arms) were tallied and compared against the outcomes reported for the three levels of interventions studied for citalopram non-responders in Sequenced Treatment Alternatives to Relieve Depression (STAR*D), published and unpublished results of PBO-controlled studies of olanzapine-fluoxetine combination (OFC) and aripiprazole augmentation, and electroconvulsive therapy (ECT).

Results: Standardized effect sizes and Numbers Needed to Treat values observed in the recent TMS trial compare favorably with the outcomes observed for the range of standard strategies studied in STAR*D and to both OFC and aripiprazole augmentation. The magnitude of the effect of TMS is approximately one half that of ECT.

Conclusions: The efficacy of TMS for patients who have not benefited from at least one course of antidepressant therapy appears to be comparable to both standard strategies now in use and atypical antipsychotic/antidepressant combinations. Although clearly less effective than ECT, TMS has clinically significant benefits and might be considered earlier in treatment algorithms.

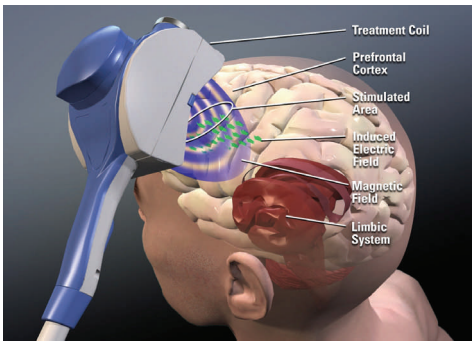
Introduction

Major depression is a common, disabling and potentially lethal illness. There are a wide variety of medications available to treat major depression, although almost all have been studied in and approved for use as initial treatments only. Unfortunately, for over two -thirds of patients, a failure to achieve clinically satisfying benefit from initial therapy is the norm. For these patients, current standard of care involves an empirical series of treatment attempts, typically using medication switches, or augmentation using antidepressants, mood stabilizers, benzodiazepines, atypical antipsychotics, or other agents.

The vast majority of clinical evidence argues that the greater the number of definitive treatment failures, the increasing likelihood of treatment non-response to subsequent interventions. The recently reported Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is the most dramatic recent example of this fact. In that work, there was a progressive likelihood of poor response with each successive treatment failure. By the time that a patient had experienced 3 treatment failures, the likelihood of remission to the fourth option fell well below 10%. It is estimated that up to 15% of depressed patients are refractory to currently available treatments. Clearly, there is a clinical urgency to identify patients who are unlikely to respond to conventional treatments and to develop effective alternatives.

Transcranial magnetic stimulation (TMS) is a non-invasive method used to electrically stimulate superficial cortical neurons, using rapidly alternating magnetic fields generated in a strong magnetic coil held in contact with the scalp (Figure 1). A large number of randomized controlled trials (RCTs), which have been aggregated in several published meta-analyses, support the antidepressant effect of TMS in patients with major depression when it is used in daily sessions over several weeks directed to the dorsolateral prefrontal cortex (DLPFC).

Figure 1. Transcranial Magnetic Stimulation



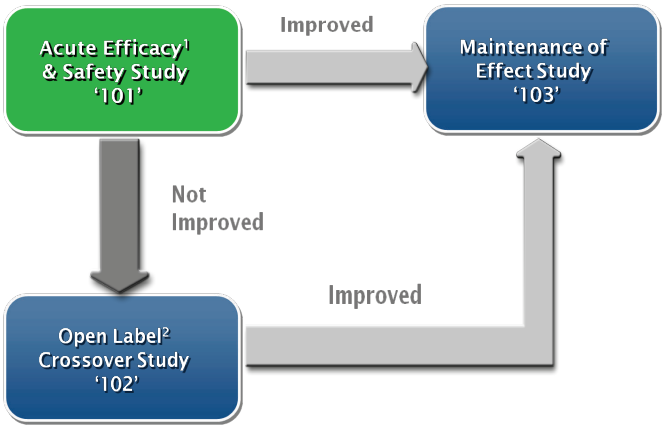
- **Pulsed magnetic fields of ~1.5 Tesla in strength**
- **Magnetic fields pass unimpeded approximately 2-3 cm into cortex**
- **Induces a focal electrical current in cortical tissue**
- **Produces local and distal functional changes on the target neural circuitry**

In two previous analyses, large clinical trial datasets were explored in order to systematically identify potential predictors of antidepressant treatment response to TMS. Using data from 195 patients across six clinical trials, Fregni, et.al., (2006) reported that younger age and less prior treatment resistance was associated with better response to TMS. In a separate study, Brakemeier, et.al., (2007) recently performed a similar analysis in an open-label treatment study of 70 patients. Consistent with the results of Fregni and colleagues, they also reported that those patients

with the least treatment resistant showed the greatest clinical benefit. We have expanded on these reports by analyzing pre-treatment predictors of outcome to treatment with TMS in our large multisite clinical trial (Lisanby et al, submitted). Consistent with the larger antidepressant clinical literature cited earlier, and the specific results for TMS described above, we replicated the observation that the best predictor of treatment response was the level of prior treatment resistance. In particular, the treatment benefit was most striking in those patients who were early in the course of their treatment resistance, namely those who had failed to benefit from one previous treatment of an adequate dose and duration in the current episode.

This abstract provides a complete summary of the efficacy outcomes observed within the treatment cohort of patients who had failed to benefit from one prior antidepressant treatment in our original randomized controlled trial. The results demonstrated that TMS is a safe and effective treatment. The patient population included in that study displayed a range of severity in the pattern of their treatment resistance prior to study entry. These data are also discussed in terms of their clinical significance by comparison to other reference datasets in the published literature for antidepressants studied in both treatment responsive and pharmacoresistant forms of major depression.

Figure 2. NeuroStar Clinical Development Program



Methods

TMS Study Device and TMS Treatment Parameters

All TMS sessions were delivered using the NeuroStar TMS Therapy System investigational device.
Treatment parameters were intended as a maximum feasible dose design. They included stimulation at 120% of observed motor threshold applied at a pulse frequency of 10 pulses per second (cycle time: 4 seconds on and 26 seconds off) for a total of 3000 pulses per treatment session.
During the acute efficacy phases of Study 101 and Study 102, TMS was administered 5 days per week for up to 6 weeks. During Study 103, TMS as an add-on rescue treatment was initiated at 2 days per week for the first 2 weeks, and then 5 days per week for the next 4 weeks.

Assessment of Prior Treatment Resistance and Methods of Analysis

Adequacy of each antidepressant treatment attempt was determined with the Antidepressant Treatment History Form (ATHF) (Prudic, et al, 1996; Sackeim, 2001). The ATHF is a reliable and validated method of rating the adequacy of antidepressant treatment trials. In particular, the ATHF has been shown to have prospective validity in predicting the outcome of future treatment based on the number of prior adequate antidepressant treatment failures. Use of the ATHF in other studies has also shown that for each adequate antidepressant treatment trial, a patient has usually experienced an average of 4 treatment attempts.

Patients who had failed only one ATHF-validated adequate antidepressant treatment in the current illness episode comprised 54.5% of the overall study population. In the current episode alone, at the time of entry into the randomized controlled trial, the one treatment failure patient population had received a median of 4 antidepressant treatments (range 1 to 23). A comparison of clinical and demographic characteristics for the subgroup of patients who had failed one previous antidepressant treatment in current episode and for the remainder of the patients in the original overall patient population is shown in Table 1.

Table 1. Subject Characteristics: Comparison of ATHF 1 vs ATHF 2-4 Study Populations

	One Adequate Antidepressant Trial Study Population (N=164)		More Than One Adequate Antidepressant Trial Study Population (N=137)	
Variable Name	Active TMS (N=88)	Sham TMS (N=76)	Active TMS (N=67)	Sham TMS (N=70)
Age in Years mean (SD)[1]	48.6 (10.8)	51.9 (9.6)	47.0 (11.3)	45.3 (10.6)
Gender - N (%) Female	 44 (50.0)	 42 (55.3)	 42 (62.7)	 32 (45.7)
Ethnic Origin N(%) - Caucasian	 81 (92.0)	 67 (88.2)	 65 (97.0)	 64 (91.4)
Depression History N(%) - Recurrent	 85 (96.6)	 74 (97.4)	 63 (94.0)	 63 (90.0)
Duration of Current Episode - Length [mean (SD)] - ≥ 2 years N(%)	 12.8 (9.9) 17 (19.3)	 11.9 (9.1) 10 (13.2)	 14.7 (10.0) 19 (28.4)	 14.4 (9.5) 12 (17.1)
Secondary Diagnoses N(%) - None - Any Anxiety Disorder	 57 (64.8) 31 (35.2)	 55 (72.4) 21 (27.6)	 39 (58.2) 28 (41.8)	 49 (70.0) 21 (30.0)
Baseline Symptom Severity [mean (SD)] - MADRS Total Score - HAMD24 Total Score - HAMD17 Total Score - IDS-SR Total Score - CGI-Severity Total Score	 32.1 (5.8) 30.0 (5.0) 22.3 (3.3) 41.3 (8.7) 4.7 (0.6)	 32.9 (6.0) 30.3 (5.0) 23.0 (3.8) 43.0 (10.3) 4.7 (0.7)	 33.7 (6.1) 30.3 (5.1) 23.0 (3.3) 42.9 (10.3) 4.8 (0.7)	 35.0 (5.1) 30.7 (4.7) 22.7 (3.3) 43.8 (9.5) 4.8 (0.7)

[1] P = 0.039 for comparison of Active TMS vs Sham TMS within One Adequate Antidepressant population
All other comparisons not significant (P > 0.05)

Methods of Analysis

Efficacy analyses were performed on the strict intent-to-treat sample of all evaluable patients, defined in the protocol as those with a baseline and at least one post-baseline observation available for analysis. The null hypothesis for primary and secondary continuous outcomes was tested with an analysis of covariance, using baseline score, and ATHF medication resistance level as fixed effect covariates, adjusting for site differences using a random effect. Categorical outcomes were analyzed using logistic regression on treatment group assignment with adjustment for site and ATHF medication resistance level. All analyses were conducted in a last-observation carried forward (LOCF) manner through the indicated time points.

Sources and Methods for Dataset Comparisons

Large summaries of FDA registration submission databases obtained by those authors under the Freedom of Information Act (Khan 2000, 2001, 2007)

- Large reference dataset of a single antidepressant medication (Thase, 2005)
- Peer-reviewed primary data publications for duloxetine, seligiline, and aripiprazole (Berman, 2007)
- STAR*D data reports and peer-reviewed publications (Fava, 2006, McGrath, 2006, Rush, 2006, Trivedi, 2006)
- UK ECT Review Group (2003)

Efficacy Parameters Compared

- MADRS or HAMD
- Continuous or Categorical Outcomes
- Effect Size (Standarized effect size – i.e. Cohen's d) for continuous measures
- Number-Needed-to-Treat (NNT) for categorical meaures

Results: Summary of Acute Efficacy

Randomized Controlled Trial (*Study 101 Results)*:

- In the overall patient population (N=301), active TMS showed superior outcomes compared to sham TMS (O'Reardon, 2007).
- An analysis of the effect sizes for clinical outcomes based on treatment resistance status in the current episode is shown in Figure 3. Patients who had failed one adequate antidepressant treatment in current episode showed a superior outcome compared to patients who had failed to benefit from 2 or more adequate treatments in current episode.
- With the majority population of patients who had experienced one adequate treatment failure in current episode (ATHF 1, N=164), active TMS showed statistically significantly superior benefit compared to sham TMS (Figures 4 and 5, MADRS data shown)

Figure 3. Standardized Effect Sizes (95%CI) by Treatment Resistance

Outcome Measure at Week 4	Overall Group (N=155 Active TMS) (N=146 Sham TMS)	**1 Adequate Treatment (N=88 Active TMS) (N=76 Sham TMS)**	2-4 Adequate Treatments (N=67 Active TMS) (N=70 Sham TMS)
MADRS	0.39 (-0.04 – 0.82)	**0.94 (0.22 – 1.68)**	-0.01 (-0.65 – 0.63)
HAMD17	0.55 (0.10 – 1.00)	**0.83 (0.20 – 1.48)**	0.42 (-0.30 – 1.15)

Effect size varies by treatment resistance as predicted from literature

Figure 4. MADRS Response Rate Outcome
Randomized Controlled Trial
One Prior AD Treatment Failure Group (N=164)

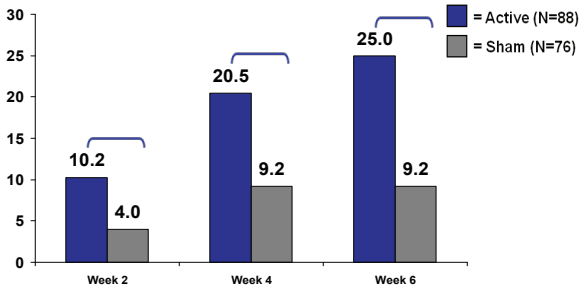
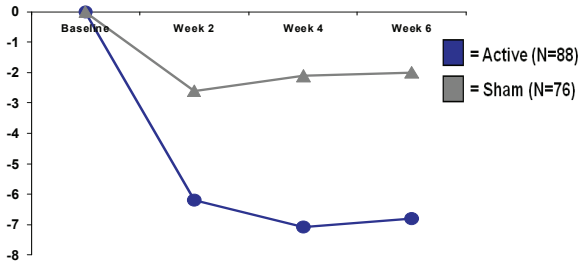


Figure 5. MADRS Mean Change from Baseline
Randomized Controlled Trial
One Prior AD Treatment Failure Group (N=164)



Open-Label Extension Trial (*Study 102 Results)*:

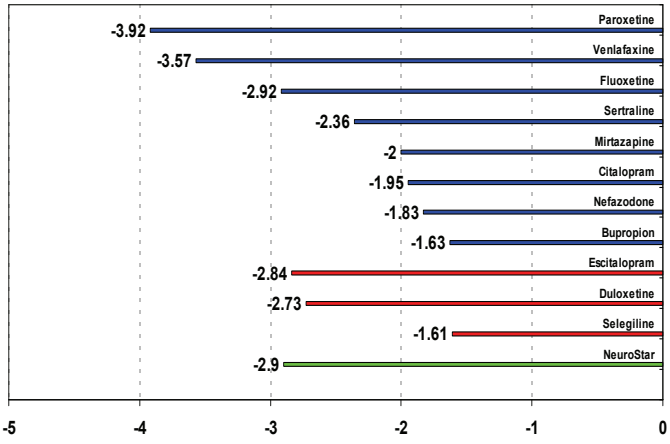
- Comparable outcomes were observed in open-label treatment in Study 102 to the results observed in Study 101 (Avery, 2008). In those patients previously allocated to sham TMS in Study 101, who had not benefited from their assigned treatment, MADRS mean change from baseline was -20.8, 95%CI [-16.9, -24.7] in the ATHF 1 subgroup compared with -13.3, 95%CI [-9.0, -17.5] in the ATHF ≥2 subgroup.
- Similar superior outcomes in the ATHF 1 patient population relative to the remainder of the study population were seen on the categorical outcome of response rate (data on file). In the ATHF 1 subgroup, 53.5% of patients achieved response by 6 weeks of active TMS, compared with 31.0% of patients in the ATHF ≥2 subgroup.

Results: Comparison with Reference Datasets

Comparison of RCT and Open-Label Outcomes with Reference Datasets:

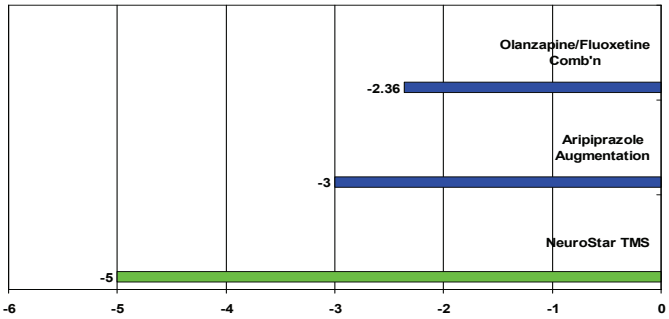
- Treatment differences between active and control conditions for TMS and pharmacotherapy is shown in Figures 6 (treatment responsive populations) and 7 (treatment resistant populations) for continuous outcome measures. Similar comparison of treatment differences for categorical outcome measures is shown in Figure 8. TMS shows absolute treatment effects that are similar or larger than the majority of approved pharmaceutical antidepressant treatment for either responsive or resistant populations.
- Effect sizes for outcomes in the TMS randomized controlled study are shown in Figure 9 (continuous outcomes, Standardized Effect Size: Cohen's d) and Figure 10 (categorical outcomes, Number-Needed-to-Treat). In each display, reference datasets are shown for both treatment responsive (Khan, 2000, Thase, 2005) or treatment-resistant study populations (Berman, 2007) for the pharmaco-therapy comparisons.

Figure 6. Comparison of Absolute Treatment Differences Between TMS and Antidepressants (HAMD17)
Treatment-Responsive Study Populations



Khan (2000; 2001; 2007); Detke (2002 a, 2002b); Goldstein (2002, 2004); Perahia (2006); Feiger (2006); Bodkin (2002)

Figure 7. Comparison of Absolute Treatment Differences Between TMS and Antidepressants (MADRS)
Treatment-Resistant Study Populations



Berman (2007); Corya (2006); Thase (2007); Shelton (2005)

Figure 8. Comparison of Absolute Treatment Differences Between TMS and Antidepressants (Response Rates)
Treatment-Responsive and Resistant Study Populations

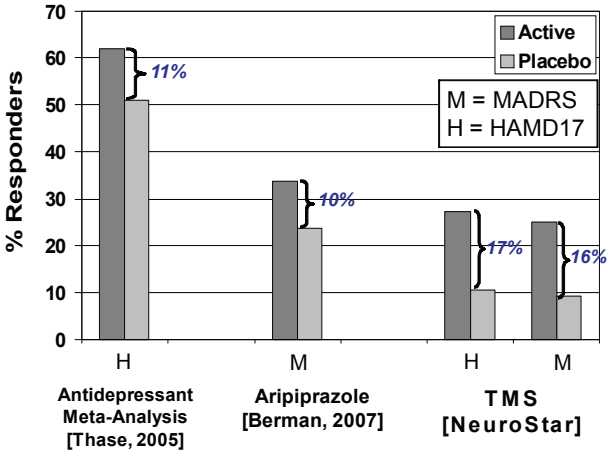


Figure 9. Standardized Effect Size (Cohen's d)
TMS Randomized Controlled Trial – Pharmacotherapy and ECT Comparison

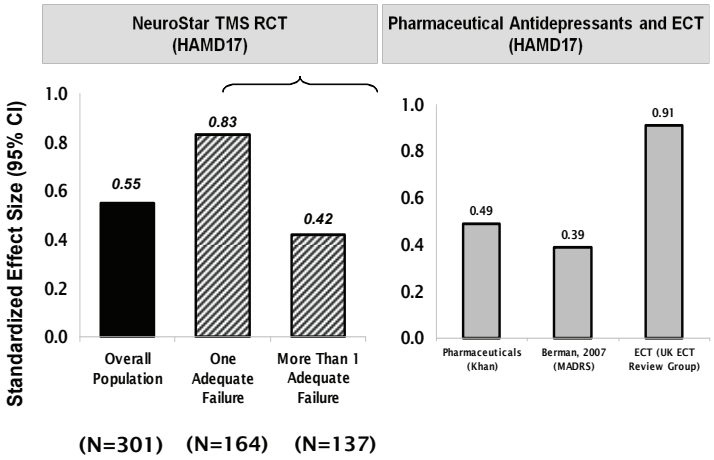


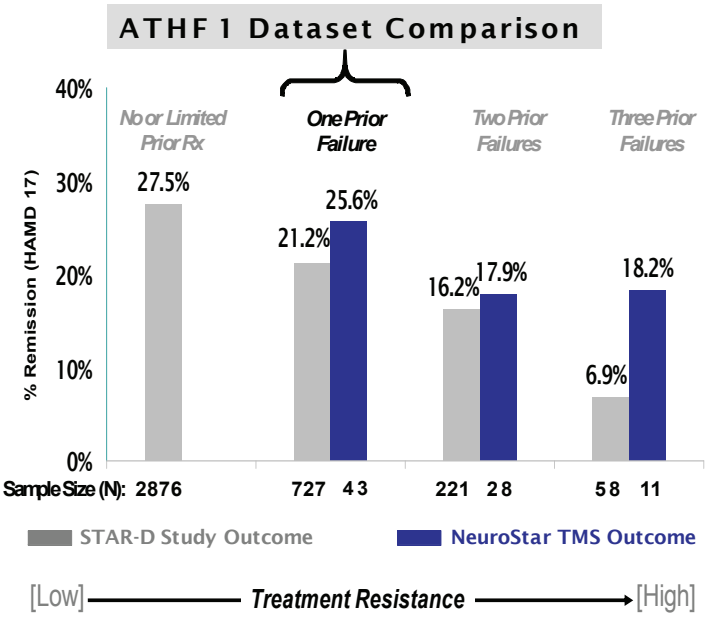
Figure 10. Number Needed to Treat (NNT)
TMS Randomized Controlled Trial – Pharmacotherapy Comparison

	NeuroStar TMS Week 4	NeuroStar TMS Week 6	Thase, 2005	Berman, 2007 Week 6
	Overall ATHF 1	Overall ATHF 1		
Response Rate (Active Treatment)	20.6% 25.0%	24.5% 27.3%	62.8%	33.7%
Response Rate (Sham/Placebo)	11.6% 10.5%	13.7% 10.5%	50.8%	23.8%
Number-Needed-to-Treat (NNT)	11.1 6.9	9.3 6.0	8.3	10.1

NOTE: For NeuroStar and Thase (2005), categorical outcomes reported for HAMD17, for Berman (2007), outcome reported only for MADRS

- Figure 11 summarizes the treatment outcomes in the TMS open-label study population against the outcomes observed in the relevant monotherapy treatment options in the STAR*D study results.
- Effect size comparisons between TMS and ECT are shown in Figure 9. In comparison to the acute efficacy RCT literature reviewed by the UK ECT Review Group, TMS demonstrates standardized effects approximately half to two-thirds as large as ECT. Figure 12 summarizes clinical outcome comparisons between TMS and ECT for acute treatment in open-label studies, and also compares the long-term durability effect for these two treatments. While the acute effects for ECT appear larger than those for TMS in these comparisons, the longer term durability of effect for TMS appears clinically favorable to that observed in long term ECT outcome studies.

Figure 11. Clinical Benefit Varies by Prior Treatment Failure in Both STAR*D and Open-Label TMS Study



Trivedi (2006), Rush (2006), Fava(2006), McGrath(2006)

Figure 12. Acute and Long-Term Outcomes

Comparison of Open-Label ECT and TMS

Study	Acute *Remission* Rate (HAMD24)	Long-Term *Relapse* Rate (HAMD24)
NeuroStar TMS Therapy		
• Study 102 Open-Label Acute	27.1% (6 week) 36.5% (9 week)	
• Study 103 Maintenance of Effect		20.5% (Med Mono + TMS)
OPT-ECT Study (N=290)	54.8%	60% (Mono Meds) 39% (Comb'n Meds)
CORE Study (N=531)	64.2%	37.1% (Cont-ECT) 31.6% (Comb'n Meds)
Community ECT Study (N=347)	46.7%	64.3% (Ad hoc)

Sackeim (2000); Prudic (2004); Kellner (2006).

Summary

- TMS is a safe and effective treatment option for patients who have failed to receive benefit from antidepressant pharmacotherapy.
- Consistent with prediction, TMS outcomes vary by prior treatment resistance, with superior outcomes in those patients at apparently earlier stages of treatment resistance.
- The outcomes observed with the NeuroStar TMS Therapy System compare favorably when considered against outcomes observed for pharmacotherapy or ECT in patients with either treatment-responsive or treatment-resistant major depression.

The TMS Therapy Study Group

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