# Treatment of Unipolar, Non-Psychotic Major Depressive Disorder with Transcranial Magnetic Stimulation: A Retrospective Evaluation Examining Acute and Long-Term Efficacy of TMS during Routine Clinical Practice.

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## Abstract

Background: According to the National Institute of Mental Health, Major Depressive Disorder (MDD) affects approximately 16.2 million lives in the U.S., or approximately 6.7% of American adults in a given year. Approximately 50% of these people seek help for this condition, and more than 30% do not receive adequate treatment from medications alone. Transcranial Magnetic Stimulation (TMS) is a noninvasive, non-systemic therapy that uses pulsed magnetic fields to induce an electric current in the brain that results in localized neuronal depolarization and beneficial effects on the symptoms of MDD. It is the purpose of this study to evaluate the standardized symptom score outcomes of TMS in routine clinical practice.

Methods: 123 patients with a primary diagnosis of unipolar, non-psychotic major depressive disorder, who had previously failed to receive benefit from a prior antidepressant treatment, received TMS treatment in a single private practice setting. Patients were assessed using the Beck Depression Inventory (BDI II) scale and Patient Health Questionnaire (PHQ-9) depression scale. Symptom score evaluations were performed prior to initiation of TMS treatment and again at the end of the acute phase of treatment. Long-term follow-up was reported on those patients that returned to the practice for assessment and are reported at time periods of 6-12 months, 12-24 months, 24-26 months, 36-48 months, and 48 months or greater.

Results: The study population included 83 (67.5%) females and 39 males, with an average age of 48.5 (range 16 – 79). The mean number of TMS treatment sessions was 40.8 (±17.6) with a range of 1,600 - 4,600 pulses administered daily (Table 1). 94 of 123 patients (76.4%) demonstrated a minimum 50% improvement in the BDI symptom score (establishing treatment response at the end of the acute phase), while 89 of 123 patients (72.4%) reported BDI symptom scores at or below 13 (establishing remission at the end of the acute phase). Total mean baseline BDI score was 25.6 (±10.1 ) and improved to a mean 10.2 (±8.7) at the end of treatment. PHQ-9 results (N=118) demonstrated similar efficacy, indicating response and remission rates of 78.8% and 52.5%, respectively. *(It is important to note that 74 of 118 patients had scores of 5 or less with 12 patients reported a rating score of 5 on the PHQ-9, missing remission by one rating point.)* Long-term data was collected on patients who achieved remission in the acute phase who were available for follow-up. We report durability results in Table 2. Scores were collected at intervals of 6-12 months, 12-24 months, 24-26 months, 36-48 months, and 48 months or greater. Long-term results demonstrate a long duration of benefit with over 80.0% of patients maintaining remission at over four years.

Discussion: In routine clinical practice, TMS shows significant improvements for treatment of Major Depression in a treatment-resistant population utilizing the Beck Depression Inventory and PHQ-9 symptom scale. In addition, long-term data further demonstrates the efficacy of TMS as a durable treatment option in a population who have failed multiple medication trials.

***Disclaimer: Abstract has been changed to reflect new data since submission.***

## Introduction

Major Depressive Disorder (MDD) is a severe and debilitating condition associated with significant morbidity and mortality. Unfortunately, more than 30% of the affected population of patients diagnosed with MDD do not respond to antidepressants. For those non-responsive patients, strategies for achieving a clinical response include antidepressant prescription change, augmentative or combination pharmacotherapies including mood stabilizers, atypical antipsychotics and/or psychotropic compounds. These options can be limited by substantial systemic adverse events.

Transcranial Magnetic Stimulation (TMS) was cleared by the US Food and Drug Administration (FDA) in 2008 for the treatment of Major Depressive Disorder (MDD) in which the patient had failed to respond to any adequate antidepressant trial in the current episode. TMS is a non-invasive, non-systemic therapeutic device that delivers magnetic resonance imaging (MRI)-strength, pulsed, magnetic fields to induce electrical stimulation of the cerebral cortex and the adjacent cortical and subcortical areas. When used as an antidepressant therapy, TMS produces a sustainable clinical benefit without the systemic adverse effects associated with psychotropic medications, or the cognitive adverse reactions commonly experienced with ECT. In a retrospective evaluation, we examined the effectiveness and safety of TMS in 123 patients treated for depression in a private practice setting between April 2010 and May 2016.

## Methods

All patients had an initial evaluation with an attending psychiatrist with a considerable knowledge of treatment-resistant depression and TMS. A history of previous antidepressant therapy was obtained, which included on average 3.9 failed antidepressant trials in the current MDD episode. TMS sessions were conducted 5 days per week with a mean of 40.8 treatments (range 20-87) per acute phase.

All treatments were initiated using the NeuroStar TMS Therapy System (Neuronetics, Inc., Malvern, PA, USA). Patients were administered one of the following protocols: the standard treatment protocol which specifies stimulation of the LDLPFC at 120% of motor threshold; pulse frequency of 10 pulses per second; cycles of 4 seconds of active stimulation followed by 26 seconds of no stimulation, 3,000 pulses; stimulation of the RDLPFC at 110% of motor threshold; pulse frequency of 1 pulse per second, 1,600 or 2,400 pulses or 4,600 total pulses (Bilateral) per treatment session. However, TMS dosing and duration of treatment varied based on clinical history, severity of disease and clinical progression. Laterality of treatment is determined at clinical evaluation and adjusted during the treatment course dependent upon patient symptoms.

The primary clinical outcomes for the treated sample were the response and remission rates at the end of the acute phase of treatment compared to baseline using the Beck Depression Inventory (BDI II) scale and the Patient Health Questionnaire (PHQ-9) depression scale. Response rates were determined based upon a minimum 50% reduction in symptom score compared to baseline for the BDI, while PHQ-9 response rates were noted as ≤ 9. Remission rates were determined by a symptom score of ≤ 13 on the BDI scale and ≤ 4 on the PHQ-9 scale . All pre-treatment, intra- and post-treatment data was input into a proprietary patient database (TMS TrakStar™) which facilitated retrospective TMS data reporting and documentation.

Secondary outcomes were post-acute phase long-term durability outcomes for those patients who achieved remission in the acute phase of treatment, based on the BDI II, who complied with follow-up visits for the time intervals reported.

## Results

Primary efficacy endpoints, Figure 1, are presented. At the end of the acute phase of treatment, patients displayed 76.4 – 78.8% response to treatment in both depression severity scores and between 52.5 – 72.4% remission. Durability data, Table 2, for those patients that were available for follow-up at the five time intervals collected, demonstrates long-term preservation of clinical benefit. 100% of patients completed treatments without complaint, non-serious or serious adverse events other than transient headache, easily managed with over-the-counter analgesics.

### Results Highlight: Long-Term Durability Data

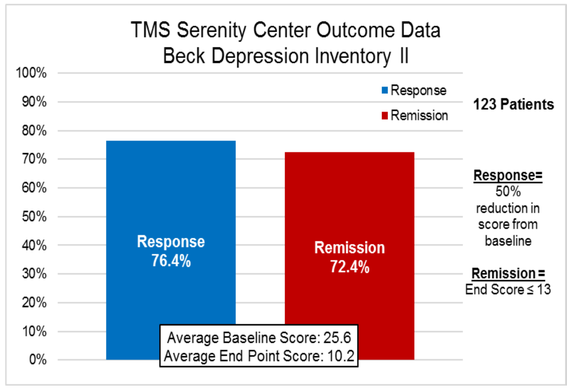
We retrospectively assessed 10 patients who achieved remission in the acute phase of treatment for long-term results based on the BDI II. Data was collected at five time intervals: 6-12 months, 12-24 months, 24-26 months, 36-48 months and 48 months or greater. The average baseline score for this patient population was 23.4 (±11.3), indicating moderate depression, with an average acute endpoint score of 5.0 (±3.0), demonstrating remission from depressive symptoms. Table 2 demonstrates the remission rates at the five time intervals. At 6-12 month interval (mean months 7.2 ±1.3), 100.0% of patients remained in remission with an average score of 3.6 (±3.5). Scores at 12-24 and 24-36 months showed similar durability, with 90.0% and 80.0% remission rates, respectively.

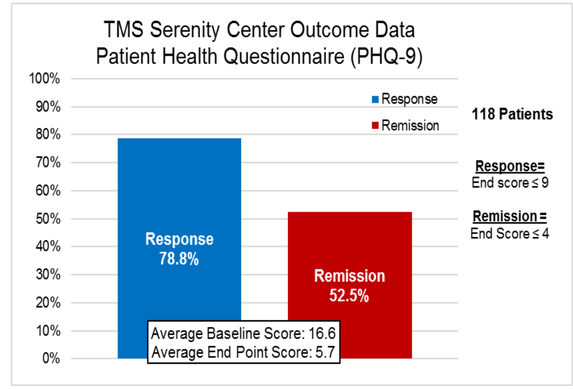
Of the 10 patients assessed at previous intervals, 6 of 10 patients provided follow-up data at the 36-48 month interval (mean months 41.8±3.9) with an average score of 3.5 (±3.1). 83.3% of patients (5 of 6) maintained remission from the end of acute phase, while one patient (score of 14 at 24 months) returned to a remitted state without the need for additional treatment, with a score of 0 at 43 months, demonstrating 100.0% (6 of 6) patients in remission. 48+ month interval data is reported in Table 2.

Our durability data demonstrates long duration of clinical benefit from the end of acute phase to over four years, further proving the efficacy of TMS therapy, both acutely and on a continued basis.

*Note: 50.0% of patients returned for re-treatment (mean 10.2 TMS sessions) between 2011 and 2016.*

### Figure 1: Primary Efficacy Outcomes for TMS in Major Depressive Disorder




### Table 1: Demographic and Clinical Characteristics of Patient Population (N=123)

| **Demographic Variables** | |
|---|---|
| N (%) females | 67.5 |
| Mean Age (years ± SD) | 48.5±14.4 |
| Age Range | 16 - 79 |
| Pharmacotherapies in current episode | 3.9 |
| Mean (SD) TMS Sessions during acute phase | 40.8 (±17.6) |
| **Baseline Symptom Score** | |
| BDI – Total score mean | 25.6 (Moderate Depression) |
| PHQ-9 – Total score mean | 16.6 (Moderately severe depression) |

### Table 2: Long-Term Durability Data (N=10)

| BDI II Symptom Scale | Acute Phase | 6 – 12 months | 12 – 24 months | 24 – 36 months | 36 – 48 months | 48+ months |
|---|---|---|---|---|---|---|
| | N= 10<br><br>Mean Acute Baseline Score (SD): 23.4 (±11.3) **indicates Moderate Depression*<br><br>Mean End Point Score (SD): 5.0 (±3.0) | N=10<br><br>Mean Symptom Score (SD): 3.6 (±3.5)<br><br>Mean Months (SD): 7.2 (±1.3)<br><br>**Remission Rate: 100.0% (10 of 10)**<br><br>**Relapse Rate: 0.0%** | N=10<br><br>Mean Symptom Score (SD): 6.7 (±7.7)<br><br>Mean Months (SD): 14.5 (±2.3)<br><br>**Remission Rate: 90.0% (9 of 10)**<br><br>**Relapse Rate: 10.0% (1 of 10)** | N=10<br><br>Mean Symptom Score (SD): 6.4 (±5.4)<br><br>Mean Months (SD): 26.6 (±3.3)<br><br>**Remission Rate: 80.0% (8 of 10)**<br><br>**Relapse Rate: 20.0% (2 of 10)** | N=6<br><br>Mean Symptom Score (SD): 3.5 (±3.1)<br><br>Mean Months (SD): 41.8 (±3.9)<br><br>**Remission Rate: 100.0% (6 of 6)**<br><br>**Relapse Rate: 0.0%** | N=5<br><br>Mean Symptom Score (SD): 5.8 (±5.1)<br><br>Mean Months (SD): 52.4 (±2.6)<br><br>**Remission Rate: 100.0% (5 of 5)**<br><br>**Relapse Rate: 0.0%** |

## Conclusion

Transcranial Magnetic Stimulation was effective and safe in the acute treatment of 123 patients recruited from our private clinical practice. Acute response and remission rates demonstrated over a 50% improvement in symptom severity, far exceeding comparable published outcomes despite the presence of a high degree of treatment resistance (mean of 3.9 failure of multiple pharmacotherapies) and co-morbidities in the treated population. Follow-up findings also demonstrated a long duration of benefit with over 80.0% of patients who provided data post-acutely maintaining remission at over four years. Lastly, no significant adverse events were experienced during or after TMS treatment. These findings further establish TMS therapy as a safe, effective and durable treatment option, both acutely and on a continued basis, for those who suffer from a high degree of symptom severity and/or do not gain relief from antidepressant medications.