Results of Transcranial Magnetic Stimulation in a Naturalistic Clinical Setting: A BioPsychoSocial Integrated Clinical Care Approach

(Naturalistic review of one hundred patients in the first private practice to provide TMS in NYC)

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INTRODUCTION

Herein we present the results of our first 100 consecutively treated patients with Transcranial Magnetic Stimulation (TMS). We were the first private practice in New York City to employ TMS which is FDA indicated for unipolar major depressive disorder.

METHODS

This retrospective study of TMS Therapy patients is unlike the pivotal study leading to FDA approval of TMS[1] and the follow-up NIH study[2] whereby our patients were allowed to remain on medications. In addition we included patients with comorbid disorders (medical and psychiatric), bipolar depression, and patients older than 65. However, patients with psychotic depression were excluded based on results of previous studies. In certain cases medications were added, decreased, or increased and psychotherapy was changed or initiated. The only absolute contraindication to treatment was if metal materials were found in the head.

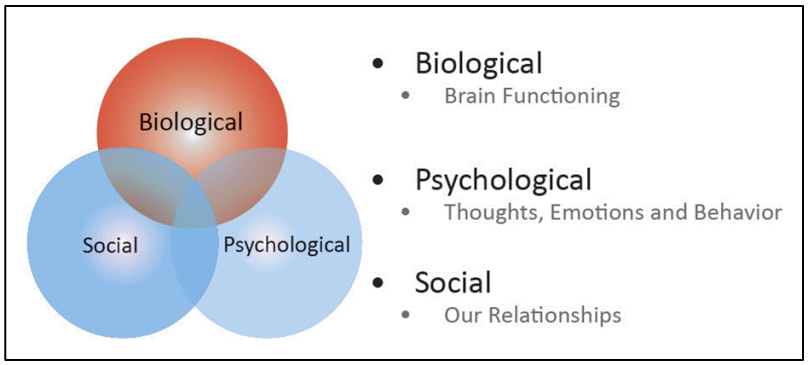
We used the Neuronetics Neurostar® TMS device for treatment. The site of stimulation was generally the Left Dorsolateral Prefrontal Cortex (LDLPC) and occasionally the Right Dorsolateral Prefrontal Cortex (RDLPC). The treatment coil was located 5.5 cm anterior to the hand area of ipsilateral motor cortex which was identified by standard methods (i.e. observing finger twitching and then employing the programmed algorithm built into the NeuroStar device). This also allows for determination of motor threshold.

Patients were treated at least 5 days per week. Following remission or plateau, patients underwent a tapering phase (treatments were reduced to 3, 2, and then 1 per week over a three week period.) Patients were allowed to read or watch TV, but not to sleep during the treatment. Also in contrast to the aforementioned studies, we varied the TMS treatment parameters. We employed frequencies of stimulation on the LDLPC ranging from 10 to 30 Hz (as compared to 10 Hz in previous trials). Pulses per session ranged from 2-5,000 (vs. 3,000[1,2]). Some patients in whom anxiety was prominent or for whom left sided high frequency TMS was too painful, were treated on the RDLPC slow (1Hz) stimulation.

Patient Undergoing TMS Treatment with the BIOPSYCHOSOCIAL Model

Right sided stimulation (RDLPC) has been shown to provide a robust antidepressant effect as well as being calming and having an anti-anxiety effect while left sided treatment tends to be activating. In certain cases patients received stimulation to the LDLPC and the RDLPC sequentially in the same session. This was termed Bilateral Simulation. Stimulation strength in terms of % Motor threshold ranged from 90 to 130% (vs. 120% in previous studies[1, 2]) on the LDLPC and 90-110% on the RDLPC depending on tolerance and response. The duration of pulses in seconds and interstimuli durations were varied according to strength (%MT) and frequency (Hz) of stimuli. Average frequency per treatment course was calculated by summing number of pulses at a given frequency over the entire course and dividing by number of pulses given in that course. We also present number of Left Sided treatments using stimulation frequency greater than 10 Hz. We present pulses per total course (addition of pulses for all sessions) as well as number of pulses per session (total number of pulses divided by treatments). Results for Left Sided treatments, Right Sided treatments and bilateral treatments are presented separately. These results, using a broad inclusion criteria and an integrated approach using the

BioPsychoSocial model, are more relevant to the real life situation of psychiatric practice than are the results of the studies alluded to above. We used several rating scales: Patients were assessed using Beck Depression Inventory (BDI) and Clinical Global Impression Scale (CGI) Patients with at least a 50% decrease in BDI and a 2-3 point change in CGI were considered Responders. A final BDI of 10 or less and a CGI of 1or 2 were required for patients to be considered remitters.



BioPsychoSocial Model
A Key Element for TMS Clinical Success

CLINICAL RESULTS

I) PATIENT POPULATION

Age Range: 15-92
- Average age: 46.8
- 16 Patients older than 65 (72 – 92)

Duration of illness prior to TMS
- Average: 3.3 years
- Range: 8 months - 40+ years

Number of Patients with Comorbid Psychiatric Disorders (N=100)
- Anxiety: 45 (OCD=4)
- Bipolar: 20
- PTSD: 15
- Axis II: 70

Number of Prior Medication Failures
- Average: 6.6
- Range: 1 - 25+

Numbers of medications
- On at commencement of TMS: 2-10+
- On at termination of TMS: 3.0

Number initiating CBT or DBT or Family Therapy
- 70 Patients

II) TREATMENT PARAMETERS

Number of Treatments
- Range 10 - 98
- Average 41

Frequency Range 10- 30 Hz

<u>Left Side</u>
- Range 10 – 30
- Average 24.5

Pulse per Treatment:

<u>Left Side</u>
- Range: 1000 – 5000
- Average: 3400

Percent Motor Threshold

<u>Left Side</u>
- Range 90 - 130
- Average 123

Treatment Laterality
- Left Sided – 72 Patients
- Right Sided – 8 Patients
- Bilateral – 20 Patients

<u>Right Side</u>
- Range (1)
- Average (1)

<u>Right Side</u>
- Range: 1000 – 3000
- Average: 2200

<u>Right Side</u>
- Range 90 - 110
- Average 96

III) TREATMENT OUTCOME

A) DROPOUTS: 8%

- Patients dropped out because of inconvenience or failure to improve.

B) COMPLICATIONS

- Patients complained of headaches or scalp tenderness particularly at initiation of treatment. Many took OTC analgesics and none dropped out because of this complaint.
- No patient had a seizure.

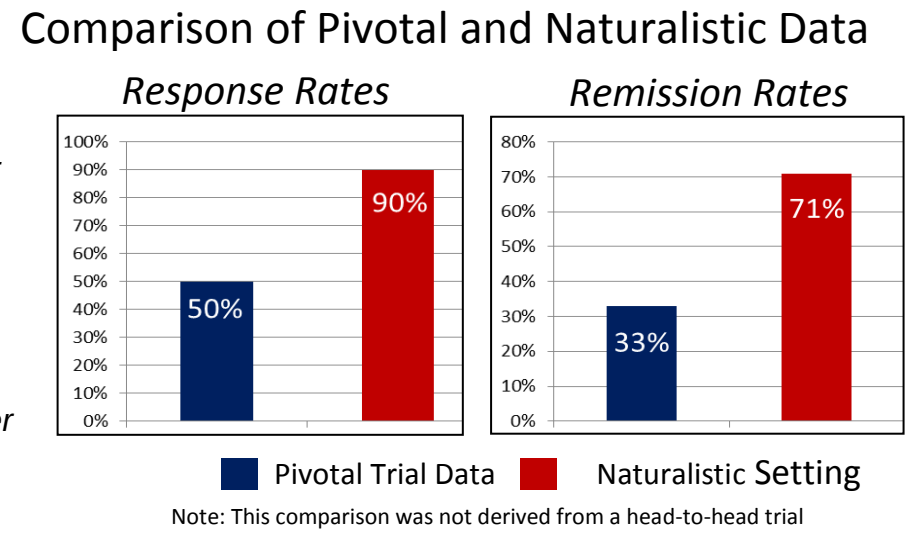
C) RESPONSES

- % Response: 90
- % Remitters: 71
- Duration of Remission:
  - Range: 8 months- 4 years, 5 months (ongoing)
  - On-going booster treatments: 30% of patients

DISCUSSION

Unique insights learned and implemented from the first 50 patients set applying to the second 50 patient set

- *Implementation of Priming.*
- *Firmer commitment to the BioPsychoSocial model including a strong recommendation for psychotherapy during treatment.*
- *TMS Education - We have tried many psycho-educational techniques from public meeting, individual psycho-education, group education, and fellow patient psycho-education. The most powerful psycho-education technique is a meeting (often spontaneous) between a patient and their trusted family member with a current TMS Therapy patient and their family. This introduction allows for those suffering to share their inner experiences and pain of depression, and for family members to share their external experiences of the impact of depression on their family and themselves. This mutual identification and shared empathy leads to increased openness to discuss and accept different psychiatric treatments. I.e. TMS Therapy.*
- *Higher confidence in safety, resulting in utilization of new and extended treatment parameters and inclusion patient with more co-morbidities compared to randomized clinical trial protocols.*
- *Earlier introduction of TMS education in patient consultation, resulting in earlier prescribing of TMS Therapy.*



Note: This comparison was not derived from a head-to-head trial

Overall [4]

- *90% responders and 71% remitters in our first 100 patients. This is consistent with data currently being presented by other TMS Providers in naturalistic setting.*

- *These results are superior to those reported in the pivotal FDA approval Study*[1] *and the NIMH sponsored trial by George*[2]*. Our results are markedly better than those obtained in the STAR*D Study*[3]*. This is despite treating patients with diagnoses excluded from these studies e.g. Bipolar Depression and patients with severe comorbid disorders.*

- *Unlike the pivotal*[1] *and George*[2] *studies in which response fell off drastically for patients who failed more than one treatment, our patients had all failed 4 or more treatments yet had a better % response and remission rate (90% response / 71% remission vs. 25% response /15% remission)*

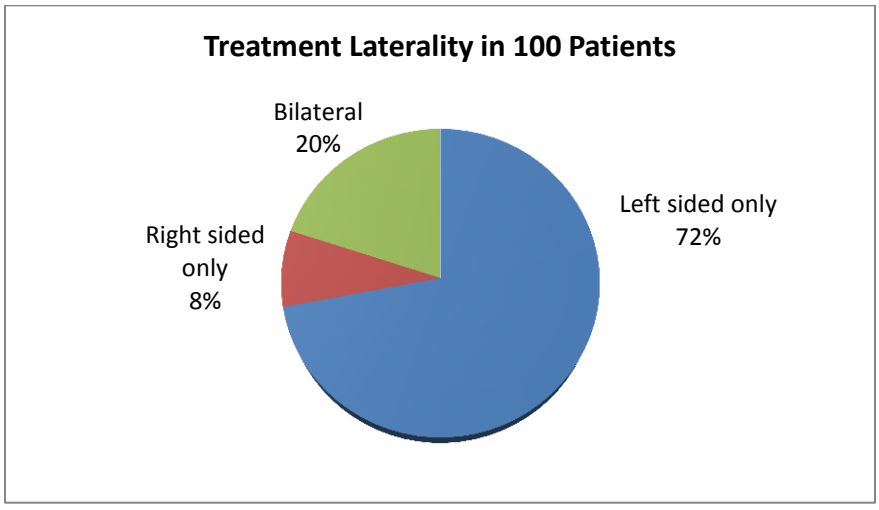
- *The treatment was tolerated extremely well despite our using parameters that exceeded those recommended. Specifically, none of our patients had seizures.*

- *Unlike the two TMS pivotal studies, our study was not placebo controlled. However, patients with this degree of treatment resistance tend to have low response rates as shown in the Star*D Study.*

- *We speculate that there is a synergistic effect between the TMS and concomitant medications. (An indirect support for this speculation is our observation of the emergence of Mania for the first time after TMS in a patient with over 20 years of depression and had been treated during this time with multiple antidepressants.)*

- *We also believe that psychotherapy (which was not allowed in the TMS studies) synergizes with TMS. This fits into the literature that demonstrates that biological and psychotherapy treatments given together are frequently additive or synergistic. George has proposed a mechanism for synergy of CBT and TMS*

- *We speculate that* ***the manner by which therapies were "laddered (i.e. added) and sequenced (i.e. in what order we additionally added BioPsychoSocial therapies in the individual patient)" contributed to increased positive outcome.*** *This fits into the literature that demonstrates that biological and psychotherapy treatments given together are frequently additive or synergistic.*



Specific factors leading to our response rate:

a. *Patients continuing their medications and/or having them changed in consultation with the referring MD.*

b. *Optimizing/enhancing/initiating psychotherapies (including CBT, DBT, Family, Couples, Psych educational, Supportive and Insight-oriented Individual).*

c. *Strongly encouraging exercise and proper nutrition.*

d. *Customizing our TMS treatment with different settings (as off label procedures). These interventions were not allowed in 1 and 2.*

e. *Providing good support for the patient and coordinated communication with the patient, family, and treating therapist where applicable.*

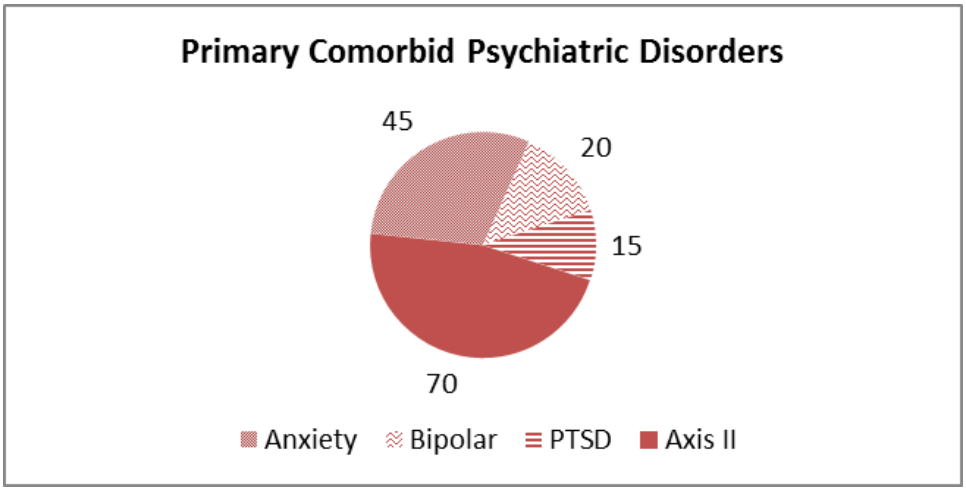
f. *Furthermore the daily supportive contact with a clinician (not allowed in studies 1 and 2) leads to increased adherence to modalities other than TMS.*

- *Further work is required to ascertain the precise contribution of each of factors a-f to our outcomes: concomitant optimizing of psychotherapies and/or pharmacology and/or alterations of parameters (which were done on an ad hoc fashion) were not allowed in pivotal studies and clinician contact was also minimized in 1, 2.*

- *We consider TMS is an innovative addition to the "psychotherapy" of Personality Disorders since by "stripping away" the symptoms, TMS allows the patients to distinguish between symptoms of their depression and their personality disorder. This allowed the patient to see the Axis II component more clearly and allowed the patient to better grapple with them.*

- *Psychotherapy seems to "flow" better during or after TMS (especially in patients with underlying or underappreciated Personality Disorders).*

- *Additionally Mark George has proposed a mechanism for TMS- CBT synergy.*



CONCLUSIONS

- ***The laddering and sequencing of TMS and pharmacology and psychotherapies in the BioPsychoSocial Approach to patients with Depression and co-morbid illnesses increases positive outcomes .****TMS is not just a mechanical tool to be administered without consideration of the overall clinical picture. TMS needs to be integrated into a patient's overall treatment plan.*

- *TMS is an excellent treatment for a broader range of patients than recommended by the FDA; and that the FDA indication is unrealistically restricting 'real world' patient clinical presentations.*

- *We believe that further research should focus on identifying the most valuable concomitant treatments (both pharmacological and psychotherapeutic) and how to choose the TMS stimulation parameters which are optimal for a given patient.*

References

1. *O'Reardon, J. P., H. B. Solvason, et al. (2007). "Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial." Biol Psychiatry 62(11): 1208-1216.*
2. *George, MS. Arc Gen Psychiatry 2010; 67 (5) 507-16*
3. *Warden, D, Rush, JA. Current Psychiatry reports 2007; 9: 449-459*
4. *Manevitz, A., Halper, J., and Kanomori, Y. Poster Results of Transcranial Magnetic Stimulation in a Naturalistic Clinical Setting: A BioPsychoSocial Integrated Clinical Care Approach. American Psychiatric Association Annual 2012 Convention.*

For More Information About:

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