Brain Stimulation 15 (2022) 226–228

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Long-term outcomes of a course of deep TMS for treatment-resistant OCD

After a multicenter randomized sham-controlled trial of Deep TMS™ therapy for obsessive-compulsive disorder (OCD) demonstrated a 38% response rate that is sustained for at least four weeks [1] the FDA granted a de novo clearance for the H7 Coil. In real-world clinical practice settings 52.4% of patients achieved at least one month sustained response [2].

There have been limited studies on the durability of pharmacotherapy for OCD and the few publications on the subject report no durability, requiring maintenance [3,4]. With regards to cognitive behavioral therapy (CBT), there are mixed results. A recent large meta-analysis of twenty-four randomized controlled trials demonstrated no durability [5]. Another study found durability after one year [6]. Yet another study demonstrated durability for a year for patients who reached remission (Y-BOCS score$\leq$12), while patients with higher post-treatment Y-BOCS (Yale-Brown Obsessive-Compulsive Scale) scores had a high likelihood of decompensating [7]. In adolescent OCD durability of up to 3 years has been reported for CBT [8]. No durability is reported for DBS since turning off the stimulator results in immediate symptom worsening [9].

To shed some light on the potential durability of Deep TMS treatment for OCD, clinical sites that participated in the OCD multicenter trial as well as those that contributed the post marketing data were contacted (n = 16). All sites were provided with a list of their patients who met response criteria at their last Y-BOCS evaluation following the Deep TMS treatment course (overall N = 108) and were compensated for contacting these patients and reporting whether each of them had, since the end of their treatment, any medication change/CBT/hospitalization/Deep TMS re-treatment. If so, on what date did the change in treatment occur and was it due to an exacerbation of the patient's OCD or due to a desire for greater improvement. Sites were also requested to inquire about functional disability, days lost and days unproductive per week. The patient populations were previously described [1,2], and the study was approved by Sterling Institutional Review Board.

The potential durability of response to Deep TMS was defined as the elapsed time from the end of the Deep TMS treatment course until a change in treatment occurred. Demographic data on the participating patients had already been recorded prior to their Deep TMS treatment course and included the following information: OCD symptom severity (Y-BOCS), functional impairment (Sheehan Disability Scale, SDS), comorbidities, age, gender, age of OCD onset, family history of OCD, number of life-time failed medications, and concomitant SRI medications. Symptom severity (Y-BOCS) had also been recorded at the end of each patient's Deep TMS treatment course as well as the number of Deep TMS sessions they received. This data allowed, beyond reporting on the average 'durability' of Deep TMS treatment for OCD, an analysis of predictors and moderators of the Deep TMS response 'durability'.

The analysis set included 60 patients from 7 centers for whom there was 'durability' data. Of those, only 8 patients (13.3%) had 'durability' of <1 year, while 52 patients (86.7%) had 'durability' of $\geq$1 year. Half of the patients who had at least 1 year 'durability' (n = 26), who represent 43.3% of the analysis set, had 'durability' of $\geq$2 years (Fig. 1B). The average 'durability' of Deep TMS for OCD was $\geq$1.98($\pm$0.13) years. Importantly, 37/60 (62%) patients were still considered to have Deep TMS 'durability' at the time of the survey (see Fig. 1A for a narrative breakdown of the data). None of the demographic or treatment information was found to be predictive of 'durability' length.

Almost half of the analysis set (n = 28) had functional disability data (SDS) as well. A significant reduction in disability was reported by patients following Deep TMS treatment. While prior to Deep TMS the self-reported unproductive days per week was on average 5.5($\pm$0.4), post treatment it was only 1.8($\pm$0.4) – an average reduction of 3.8($\pm$0.4; $p < 5^{-9}$). The decrease in lost days per week was also statistically significant, with reports of an average of 1.9($\pm$0.6) prior to Deep TMS vs. 0.3($\pm$0.2) post treatment – an average reduction of 1.8($\pm$0.5; $p < 0.001$) (Fig. 1C). A significant correlation was found between the improvement in symptom severity (i.e., reduction in Y-BOCS from baseline) to the functional improvement (i.e., reduction in weekly unproductive days) following Deep TMS treatment ($r = 0.45$, $p = 0.018$) (Fig. 1D).

It has been previously demonstrated that Deep TMS therapy is an effective treatment for OCD patients who have failed multiple medications [10], alluding to a different mechanism of action. The 'durability' results demonstrated here reaffirm that the mechanism of Deep TMS treatment in OCD is different from that of medications that necessitate chronic use. The mechanism of Deep TMS is likely based on direct modulation of the cortical-striatal-thalamic-cortical circuitry, specifically through up-regulation of the Anterior Cingulate Cortex (ACC) [1,11]. A recent 1H-MRS study found significant increases in levels of NAA, Choline and Creatine in the ACC following Deep TMS in OCD patients, indicating direct neural stimulation of this region [12]. A recent modelling study found that Deep TMS induces significant electric field in various deep structures including the ACC [13].

As with any registry-based study, the primary limitations to ours are incomplete data due to a lack of follow up or continued care with the Deep TMS provider after the treatment course. Many patients only went to the Deep TMS center for the treatment and not their ongoing psychiatric care, which limited the analysis set to 60/108 responders and 7/16 centers. Furthermore, as the Y-

https://doi.org/10.1016/j.brs.2021.12.011

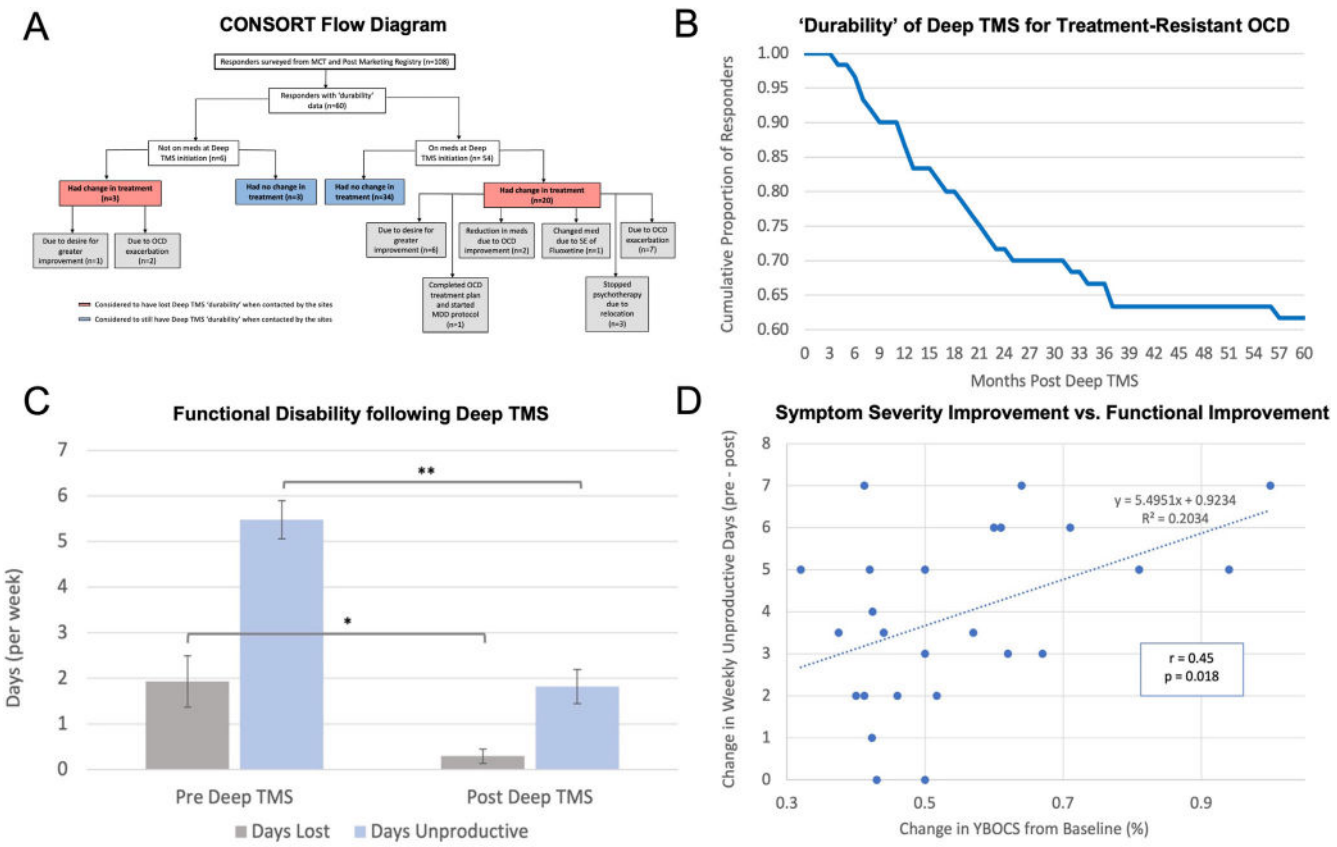

Fig. 1. 'Durability' of Response and Functional Disability following Deep TMS™ **for Treatment-Resistant OCD.** (A) CONSORT flow diagram presenting a narrative breakdown of the available data. (B) Kaplan-Meier survival curve of cumulative 'durability' of response to Deep TMS for OCD, where 'durability' is defined as time since Deep TMS without change in treatment for patients who met response criteria at their last Y-BOCS evaluation after the Deep TMS course. (C) Functional disability presented as days lost (grey bars) and days unproductive (blue bars) per week pre and post Deep TMS (left and right, respectively). Asterisks denote statistical significance: *-$p<0.001$, **-$p<5^{-9}$. (D) Scatter plot presenting correlation across patients between change from baseline in functional disability (weekly unproductive days) and in symptom severity (Y-BOCS score) following Deep TMS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

BOCS is not used in routine clinical practice, this resulted in a 'durability' definition as elapsed time from the last Deep TMS session until any change in treatment was necessary. Ideally, this would be corroborated by Y-BOCS scores, a more standardized metric administered every few months. Confirmatory and mechanistic studies investigating the response 'durability' of Deep TMS therapy for OCD with standardized measures are warranted.

Funding

BrainsWay Ltd.

Declaration of competing interest

Tal Harmelech is a BrainsWay employee. Aron Tendler is the Chief Medical Officer of BrainsWay and has a financial interest in BrainsWay as well as a commercial clinical and research TMS center. He has received speaking fees from BrainsWay, Neuronetics and the Clinical TMS Society. Yiftach Roth is a key inventor of the Deep TMS technology, Chief Scientist at BrainsWay and has a financial interest in BrainsWay.

References

[1] Carmi L, Tendler A, Bystritsky A, et al. Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatr 2019. https://doi.org/10.1176/appi.ajp.2019.1810. appi.ajp.2019.1.

[2] Roth Y, Tendler A, Arikan MK, et al. Real-world efficacy of deep TMS for obsessive-compulsive disorder: post-marketing data collected from twenty-two clinical sites. J Psychiatr Res 2021;137:667–72. https://doi.org/10.1016/j.jpsychires.2020.11.009.

[3] Pato MT, Zohar-Kadouch R, Zohar J, et al. Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatr 1988;145(12):1521–5. https://doi.org/10.1176/ajp.145.12.1521.

[4] Leonard HL, Swedo SE, Lenane MC, et al. A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatr 1991;48(10):922. https://doi.org/10.1001/archpsych.1991.0181.

[5] Fisher PL, Cherry MG, Stuart T, et al. People with obsessive-compulsive disorder often remain symptomatic following psychological treatment: a clinical significance analysis of manualised psychological interventions. J Affect Disord 2020;275:94–108. https://doi.org/10.1016/j.jad.2020.06.019.

[6] Nadeem MJ, Chan E, Drummond L. A naturalistic study of the maintenance of gains made with treatment of patients with profound treatment-refractory obsessive-compulsive disorder. Front Psychiatr 2021;12:1209. https://doi.org/10.3389/fpsyt.2021.673390.

[7] Elsner B, Wolfsberger F, Srp J, et al. Long-Term stability of benefits of cognitive behavioral therapy for obsessive compulsive disorder depends on symptom remission during treatment. Clin Psychol Eur 2020;2(1):1–18. https://doi.org/10.32872/cpe.v2i1.2785.

[8] Melin K, Skarphedinsson G, Thomsen PH, et al. Treatment gains are sustainable in pediatric obsessive-compulsive disorder: three-year follow-up from the NordLOTS. J Am Acad Child Adolesc Psychiatry 2020;59(2):244–53. https://doi.org/10.1016/j.jaac.2019.01.010. Epub 2019 Feb 14. PMID: 30768383.

[9] de Koning P, Figee M, Endert E, et al. Rapid effects of deep brain stimulation reactivation on symptoms and neuroendocrine parameters in obsessive-compulsive disorder. Transl Psychiatry 2016;6:e722. https://doi.org/10.1038/tp.2015.222.

[10] Roth Y, Barnea-Ygael N, Carmi L, et al. Deep transcranial magnetic stimulation for obsessive-compulsive disorder is efficacious even in patients who failed multiple medications and CBT. Psychiatr Res 2020;290:113179. https://doi.org/10.1016/j.psychres.2020.113179.
[11] Carmi L, Alyagon U, Barnea-Ygael N, et al. Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimul 2018;11(1):158–65.
[12] Reddy S, Goyal N, Shreekantiah U. Adjunctive deep transcranial magnetic stimulation (dTMS) in obsessive compulsive disorder: findings from 1 H magnetic resonance spectroscopy. Asian Journal of Psychiatry 2021;62:102721.
[13] Gomez-Tames J, Hamasaka A, Hirata A, et al. Group-level analysis of induced electric field in deep brain regions by different TMS coils. Phys Med Biol 2020;65:025007.

Tal Harmelech*
BrainsWay Ltd., 19 Hartum St. Har Hotzvim, Jerusalem, 9777518, Israel

Aron Tendler
BrainsWay Ltd., 19 Hartum St. Har Hotzvim, Jerusalem, 9777518, Israel

Advanced Mental Health Care Inc., 1903 Southern Blvd. Royal Palm Beach, FL, 33411, USA

Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben Gurion University of the Negev, Beer Sheva, Israel

Mehmet Kemal Arikan, Hamide Laçin Çetin, Muhammed Taha Esmeray, Reyhan Ilhan
Akademik Psychiatry & Psychotherapy Center, Halaskargazi Cad. No: 103, Gün Apt, apartment: 4B, 34371, Osmanbey, Istanbul, Turkey

Ryan Vidrine
Mindful Health Solutions, 360 Post Street, Suite #500, San Francisco, CA, 94108, USA

Owen Muir, Carlene MacMillan, Rebecca Sinclair
Brooklyn Minds, 347 Grand St, Brooklyn, NY, 11211, USA

Saad Shakir
Silicon Valley TMS, 2039 Forest Ave STE 201, San Jose, CA, 95128, USA

David Kent
NuMe TMS, 2375 S Cobalt Point Way #102, Meridian, ID, 83642, USA

Nicholas Evangelidis
Katie's Way, 720 Poyntz Avenue, Manhattan, KS, 66502, USA

Yiftach Roth
BrainsWay Ltd., 19 Hartum St. Har Hotzvim, Jerusalem, 9777518, Israel

Department of Life Sciences and the Zlotowski Center for Neuroscience, Ben Gurion University of the Negev, Beer Sheva, Israel

* Corresponding author.
E-mail address: tal.harmelech@brainsway.com (T. Harmelech).

30 November 2021
Available online 1 January 2022