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Original article

Factors associated with response after deep transcranial magnetic stimulation in a real-world clinical setting: Results from the first 40 cases of treatment-resistant depression

K. Feffer [a], K.A.B. Lapidus [b], Y. Braw [c], Y. Bloch [a], S. Kron [a], R. Netzer [d], U. Nitzan [a,*]

[a] Shalvata Mental Health Center, Hod-Hasharon, Sackler School of Medicine, Tel-Aviv University, P.O.B 94, Tel-Aviv, Israel
[b] Northwell Health Department of Psychiatry, Lenox Hill Hospital, New York, NY, USA
[c] Department of Behavioral Sciences, Ariel University, Ariel, Israel
[d] Shalvata Mental Health Center, Hod-Hasharon, Tel-Aviv, Israel

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ABSTRACT

Background: Deep transcranial magnetic stimulation (dTMS) has been sanctioned by the United States Food and Drug Administration for treatment-resistant depression. In a retrospective cohort study, we evaluated response and effectiveness of dTMS in real-world practice, as an add-on treatment for resistant depression.

Methods: Forty adult outpatients suffering from depression, all taking psychiatric medications, underwent 20 dTMS treatments over a 4–6 week period. At baseline (T0), visit 10 (T1), and visit 20 (T2), the Clinical Global Impression-Severity (CGI-S) scale was administered, and the Clinical Global Impression Improvement (CGI-I) scale was completed at T1 and T2; the Hamilton Depression Rating Scale (HDRS-21) was administrated at T0 and T2 only. The patients also completed the Quick Inventory of Depressive Symptoms–Self-Report (QIDS-SR) at T0, T1, and T2.

Results: Depressive symptoms (HDRS-21 total score) decreased significantly following treatment. The HDRS total score decreased from an average of 21.22 (± 6.09) at T0, to 13.95 (± 7.24) at T2. Correspondingly, at T2, 32.5% were responders to the treatment and 20% were in remission, based on the HDRS-21. Treatment was well tolerated, with a discontinuation rate of 7.5%. While depressive symptoms at baseline did not predict remission/response at T2, higher HDRS scores at T0 were associated with a larger *decrease* in depressive symptoms during the study.

Conclusions: Significant antidepressant effects were seen following 20 dTMS treatments, given as augmentation to ongoing medications in treatment-resistant depression. The findings suggest that among patients with TRD, the severity of the depressive episode (and not necessarily the number of failed antidepressant medication trials) is associated with a positive therapeutic effect of dTMS. Hence, the initial severity of the depressive episode may guide clinicians in referring patients for dTMS.

1. Introduction

Deep transcranial magnetic stimulation (dTMS) has been sanctioned by the United States Food and Drug Administration (FDA) since 2013 for treatment-resistant depression (TRD). This therapy is also authorized for use in the treatment of major depressive disorder (MDD) in Israel (since 2013) and Europe (since 2014) as an add-on or monotherapy. The dTMS device (Brainsway Ltd., Jerusalem, Israel) utilizes a unique coil design, the H-coil, that permits the stimulation of deeper and larger brain volumes compared to standard TMS coils [1,2]. The H-coil induces an effective magnetic field to a depth of 3–6 cm [1], which can reach subcortical areas, compared to a depth limit of about 1.5 cm when using a standard TMS coil. Recent studies of alcohol use disorders [3,4] provide additional indirect evidence that dTMS can stimulate deep brain structures, including those related to the reward pathway. Evidence from several industry-sponsored trials supports the efficacy of dTMS, applied to the left dorsolateral prefrontal cortex, in the treatment of unipolar and bipolar depression [5,6]. Recently, Levkovitz et al. [7] published the results of a large prospective multicenter randomized-controlled-trial (RCT) that was performed prior to the FDA approval. In this

* Corresponding author. Fax: +972 3 5496872.
E-mail address: urini@clalit.org.il (U. Nitzan).

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study, response and remission rates were significantly higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, $P = 0.013$; remission: 32.6 vs. 14.6%, $P = 0.005$), and active dTMS was associated with a mean improvement of 6.39 points on the Hamilton Depression Rating Scale (HDRS). Eligible subjects were adult outpatients (DSM-IV diagnosis of MDD), antidepressant medication-free, that were required to have failed at least one but no more than four adequate antidepressant treatments or to have had intolerance to at least two antidepressants in the current episode. Evidence from both industry-sponsored and academic studies is accumulating about the benefits of dTMS in treating depression. A recent meta-analysis of nine open-label studies has demonstrated similar rates of remission (29%), with a higher response rate, in patients that received concurrent antidepressants medications [8], and marked anxiolytic effects regardless of concurrent treatments [9]. Another meta-analysis demonstrated improvement in depressed patients' cognitive function after a 20-session course of high-frequency dTMS [10].

When introducing a new therapeutic intervention, such as dTMS, the translation of the findings from controlled studies into real-world practice is of paramount importance. There are some important differences that can be expected. Primarily, in clinical use dTMS would most likely serve as augmentation for antidepressant medications. In addition, the efficacy of dTMS has not been examined in patients with high levels of resistance to medication (>4 failed antidepressant trials). This group of patients is likely to seek and be referred for dTMS, rather than being managed with only additional antidepressant medications. These patients are also more likely to be willing to withstand the technical demands and economic burden involved in this kind of treatment. Finally, a study without industry sponsorship serves to further establish the clinical utility of dTMS in treating TRD.

We provided treatment with dTMS to adult outpatients with TRD ($n = 40$) in an academic medical center. The patients remained on psychiatric medications, presented with various medical and psychiatric comorbidities, and had failed or could not tolerate a variety of antidepressant trials in their current affective episode (4.8 ± 2.8). The aim of this retrospective study was to assess the effectiveness of dTMS in the management of TRD in a real-world setting.

We hypothesized that dTMS would be less effective in relieving symptoms of TRD in the setting of "real-world" clinical practice' compared with the earlier RCT [7]. This was based on the expected comorbidities, severity of psychopathology and level of treatment resistance in our population, and despite the higher placebo effect anticipated in an open-label design.

In addition to assessing efficacy, we performed exploratory analyses in order to examine demographic (e.g., age and gender) and clinical (e.g., depression severity and level of treatment resistance) measures that might be associated with treatment response.

2. Methods

2.1. Participants

This was a retrospective cohort study of 40 adult outpatients (≥ 18 years) treated for depression in the dTMS clinical unit at the Shalvata Mental Health Center. Patients had a DSM-IV-TR [11] diagnosis of MDD ($n = 32$) or bipolar disorder (BD; $n = 8$) and were currently in a major depressive episode with a total HDRS-21 total score of at least nine (mild depression). The duration of patients' current episode was at least three months and all patients could not tolerate or failed to respond to at least two antidepressant trials of adequate dose and duration during the current episode. Exclusion criteria were: active psychosis, mental retardation, and major neurological disorder/s. Contraindications for treatment were metal head implants and history of seizures. Treatment was self-paid, and took place between August 2012 and December 2014.

2.2. Study overview

A systematic medical chart review was conducted for the first 40 consecutive dTMS patients. At screening, all patients had a complete psychiatric and medical evaluation by an attending psychiatrist with expertise in TRD and dTMS. Demographic and clinical variables were collected using questionnaires and electronic medical records. These included the patients' history of antidepressant trials and psychiatric, physical, and substance use comorbidities. The Maudsley Staging Model (MSM) was used to quantify treatment resistance in depression; this model yields scores ranging from minimal (3) to severe resistance (15) based on treatment history, severity of illness, and duration of presenting episode [12]. Treatment with dTMS was adjunctive; all patients were continued on medications and pre-dTMS medications were maintained at fixed doses whenever possible. The dTMS treatment, as well as common side effects, were discussed before patients provided informed consent to be treated in the dTMS unit. Patients were free to withdraw without consequence at any time from the dTMS treatment.

Twenty dTMS treatments were provided, 3–5 sessions per week for 4–6 weeks, in agreement with labeled use. At baseline, all patients completed the Mini International Neuropsychiatric Interview (MINI) 6.0 screen, and then underwent a full clinical psychiatric assessment including multi-axial diagnosis by a senior psychiatrist (additional clinical assessments were performed at visits 10 and 20). At baseline (T0), visit 10 (T1), and visit 20 (T2), the Clinical Global Impression-Severity (CGI-S) scale was administered. The Clinical Global Impression Improvement (CGI-I) scale was administered at T1 and T2. The Hamilton Depression Rating Scale (HDRS-21) was administered at T0 and T2 only. The patients also completed the Quick Inventory of Depressive Symptoms–Self-Report (QIDS-SR) at T0, T1 and T2. On each treatment day, side effects were assessed and documented by a medical practitioner using free, unsolicited reporting.

2.3. Deep TMS treatment

A trained medical assistant, skilled in the administration and operation of dTMS, delivered the treatments. A senior psychiatrist was available at all times during the procedure. Accepted safety guidelines were followed, including the availability of hearing protection, mouth guards, first aid, and anticonvulsant medication. The optimal position on the scalp for stimulation of the right abductor pollicis brevis muscle was identified, and the individual motor threshold (MT) was determined by delivering single pulses of stimulation to the motor cortex. The exact threshold was determined by gradually increasing the intensity (using single pulse mode, applying one pulse every 5 seconds), until movement was observed. After defining the motor threshold, the coil was moved 5 cm anterior to the most sensitive motor location (in order to position it over the left dorsolateral prefrontal cortex). At each session, dTMS was applied to the prefrontal cortex at an intensity of 120% of the MT with a frequency of 18 Hertz (Hz), using train duration of two seconds (55 pulses per train) and an inter-train interval of 20 seconds. The number of magnetic pulses per session was 1980 and the duration of each treatment was approximately 20 minutes. The Brainsway dTMS system was used to provide treatment.