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Real world efficacy and safety of various accelerated deep TMS protocols for major depression

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ABSTRACT

There is growing interest in accelerated rTMS dosing regimens, wherein multiple sessions of rTMS are applied per day. This Phase IV study evaluated the safety, efficacy, and durability of various accelerated Deep TMS protocols used in clinical practice. Data were aggregated from 111 patients with major depressive disorder (MDD) at 4 sites. Patients received one of several accelerated Deep TMS protocols (2x/day, 3x/day, 5x/day, 10x/day). Self-assessment questionnaires (PHQ-9, BDI-II) and clinician-based rating scales (HDRS-21, MADRS) were collected. On average, accelerated TMS led to an 80.2% response and 50.5% remission rate in the first month based on the most rated scale for each patient. There was no significant difference between protocols (Response: 2x/day:89.6%; 3x/day:75%; 5x/day:81%; 10x/day:67.6%). Response occurred after 10 (3x/day), 20 (5x/day), and 31 sessions (10x/day) on average– all of which occur on day 3–4 of treatment. Of patients with longer term follow up, durability was found in 86.7% ($n = 30$; 60 days) and 92.9% ($n = 14$; 180 days). The protocols were well-tolerated with no reported serious adverse events. Accelerated Deep TMS protocols are found to be safe, effective therapeutic options for MDD. They offer treatment resistant patients a treatment option with a rapid onset of action and with long durability.

1. Introduction

Major depressive disorder (MDD) is a prevalent disorder associated with significant negative effects on health and a high economic burden (Gorman et al., 1996; Kesler et al., 2003; Lopez et al., 2006; Whiteford et al., 2013). While many pharmacotherapeutic options are available, up to 30% of patients with MDD do not respond well to pharmacotherapy (Crown et al., 2002; Rush et al., 2006). Repetitive transcranial magnetic stimulation (rTMS) is one of the leading non-pharmacotherapeutic interventions for MDD. Initially cleared for use by the FDA in 2008, TMS is now widely used as a therapeutic approach for patients that do not respond well to pharmacotherapy. (Lefaucheur et al., 2020; Fitzgerald et al., 2021). Deep TMS™ is a form of TMS that utilizes specially designed H—Coils to induce neuronal depolarization in deep and broad cortical regions (Roth et al., 2002; Zibman et al., 2021). The safety and efficacy of Deep TMS for MDD have been demonstrated in randomized, controlled trials (RCTs) (Levkovitz et al., 2015; Filipcic et al., 2019), as well as in real-world post-marketing studies (Tendler et al., 2023). When administered in accordance with the FDA-cleared protocol, a single session of Deep TMS is administered once a day, five days a week, for the first four weeks, followed by optional two times per week for the next 12 weeks. This leads to 44 sessions of Deep TMS being delivered over 16 weeks.

While this dosing schedule for Deep TMS has been broadly adopted,

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there has been growing momentum in the TMS field at-large for condensing treatment into a shorter time frame (Baeken et al., 2018; Chen et al., 2020; Blumberger et al., 2021; Cole et al., 2020, 2022; for a recent review see Caulfield et al., 2022, Chen et al., 2023). For this article and like others (Caulfield et al., 2022), we are describing anything more than one session of TMS per day (which is the current standard of care) to be "accelerated" TMS dosing. In 2007 Loo and colleagues were the first to examine accelerated dosing. In 38 patients with moderate depression, they demonstrated that two sessions of TMS (delivered with a Figure-8 coil over a two-week period; 20 sessions total) led to significantly greater improvement in depression symptoms than sham, and that improvement continued over the next six weeks of a single session of TMS per day (Loo et al., 2007). A decade later in 2018, Fitzgerald and colleagues published the first larger study directly comparing accelerated dosing to one session per day (Fitzgerald et al., 2018). In that study 115 individuals were randomized to receive either an accelerated schedule (3 sessions per day) or traditional dosing (1 session per day). There were no significant differences in the efficacy of these two dosing protocols, underscoring the potential value of delivering TMS in an accelerated manner.

In 2022 the TMS field saw the first FDA clearance for a unique form of accelerated TMS as a tool for treatment resistant depression. This protocol is a particularly aggressive accelerated TMS dosing schedule-10 sessions per day over a 5-day period (Williams et al., 2018). A sham-controlled trial of 32 individuals demonstrated that individuals receiving active accelerated TMS (which also utilized functional-connectivity based targeting) was significantly more effective at reducing depressive symptoms than sham. (Cole et al., 2022) Importantly, there were no serious adverse events.

There have now been many studies that have evaluated a variety of accelerated TMS dosing schedules (see Caulfield et al., 2022, Chen et al., 2023), but little data has been published specifically on the efficacy of accelerated Deep TMS (Filipčić et al., 2021). That said, many Deep TMS providers have already begun performing accelerated Deep TMS in an outpatient setting for their patients (Tendler et al., 2018). The goal of this study was to gather data on the response and remission rates of various accelerated Deep TMS protocols as well as the onset of clinical improvement and long-term durability of clinical effects in resistant MDD patients.

2. Methods

The study was designed to collect treatment information, demographic data, and outcome data, on patients treated with the Deep TMS H1 Coil for MDD. Deep TMS clinics that offer accelerated Deep TMS treatments were asked to participate and sent instructions. Depression severity was assessed by the 21-items Hamilton Depression Rating Scale (HDRS-21, Cusin et al., 2010), the Montgomery-Asberg Depression Rating Scale (MADRS, Cusin et al., 2010), the Patient Health Questionnaire-9 (PHQ-9, Kroenke et al., 2001) and the Beck Depression Inventory-II (BDI-II, Wang and Gorenstein, 2013). Baseline assessments were done typically on the day of the first treatment visit or 1 day before. To incentivize participation and support the work of data entry, clinics were offered compensation to participate. All sites received device training and certification. The protocol was reviewed by Sterling IRB and granted exemption from informed consent provided patients were assigned only a patient code (not name/initials) and age (year, not date of birth).

2.1. Participants

Accelerated Deep TMS data were collected from 145 individuals with treatment resistant major depression (failed 5.2 ± 3.5 lifetime medications (mean±SD)) from 4 clinical sites. Participants were all seeking treatment for primary major depressive disorder, allowing psychiatric and medical co-morbidities, but no formal diagnostic assessment beyond a psychiatric interview was conducted. To be included in the analysis, all patients had to complete at least 20 sessions of Deep TMS and have at least two measurements on eligible clinician or self-report clinical scales.

2.2. Interventions

Deep TMS was administered using the BrainsWay H1 Coil with a Magstim Rapid2 (Magstim Company, Spring Gardens, UK) stimulator or with the BrainsWay 104 stimulator (BrainsWay, Jerusalem, Israel). Accelerated TMS dosing protocols were binned into 4 common dosing regimens for analysis: 2x/day, 3x/day, 5x/day, 10x/day with a minimum of 50minutes between sessions. Most patients were treated with intermittent theta burst stimulation (iTBS; 97%). The iTBS protocol consisted of bursts of 3 pulses at 50 Hz, 5 Hz bursts frequency, 2 s on and 8 s off at 80 or 90% of the hand resting motor threshold (rMT). This was typically delivered for 1800 pulses per session (88% of patients) (like Cole et al., 2022; Cheng et al., 2016; Li et al., 2020). Alternative protocols included 600 pulses/session (9%) (like Blumberger et al. 2018, Huang et al., 2005) and standard high frequency Deep TMS (3%): 18 Hz, 120% rMT intensity, 55 trains of 2 s duration, inter-train interval (ITI) 20 s, 1980 pulses per session.

2.3. Assessments and definition of core measures

As accelerated rTMS dosing paradigms are a topic of growing interest in the clinical research field, the purpose of this study was to determine if the response and remission rates from these naturally emerging protocols are comparable to established response and remission rates from traditional 1x/day Deep TMS. To address this question, the primary analysis aggregated data from all accelerated dosing regimens being used presently.

The primary endpoint was 1 month response and remission rates. This was done first on the whole dataset and was followed by a secondary subgroup analysis of response and remission rates comparing 2x/day, 3x/day, 5x/day, and 10x/day. Additionally, we recorded the median number of sessions and treatment days until remission/response for the whole datasets and for each sub-group.

The secondary endpoint was durability of the response. This was calculated at 60, 90, and 180 days after achieving response based on the scale most used in an individual patient. Rates were calculated as the number of patients showing response on all available measurements over the defined period following response, divided by the number of patients with at least one measurement at the end of the defined period following response. Analyses were carried out using GraphPad Prism Version 5.03.

3. Results

3.1. Demographic and baseline characteristics

The subjects' demographic and clinical data are shown in Table 1. Females comprised 54.7% of the sample, and the mean (SD) age was 38.9 (16.8) years. Comorbidities were reported for 19 out of 25 patients for whom the data was available. Eighty-one (77.9%) of patients had severe depression (defined as HDRS-21>22; PHQ-9>15; BDI-II>29;

Table 1
Demographic and baseline characteristics.

Characteristic ($N = 137$)	Values
Age [years], Mean (SD)	38.9 (16.8)
Women, No. (%)	75 (54.7%)
Race : Cauacasian No. (%)	35 (97.2%)
Baseline BDI-II, Mean (SD)	34.5 (10.6)
Baseline PHQ-9, Mean (SD)	19.2 (4.7)

MADRS>34), nineteen (18.3%) had moderate depression (defined as 15<HDRS-21<23; 9<PHQ-9<16; 19<BDI-II<30; 19<MADRS<35), and four (3.8%) patients had mild depression at baseline (defined as 10≤HDRS-21<16; 4<PHQ-9<10; 13<BDI-II<20; 7≤MADRS<20).

3.2. Response and remission rates

One hundred eleven patients were included in the analyses. The treatment was well-tolerated with no reported serious adverse events. Forty-eight patients received 2 sessions/day for an average of 29 treatment days administered typically every other day. Eight patients received 3 sessions/day for an average of 8 days given typically every 3–4 days. Twenty-one patients received 5 sessions/day for 6–7 days administered typically every other day. Thirty-four patients were treated with 10 sessions/day for 5 consecutive days. There was no difference in baseline severity among the 4 groups ($p = 0.62$; one-way ANOVA).

Overall patients had an 80.2% response and 50.5% remission rate on their most rated scale (Table 2; Fig. 1). Chi-square comparison between the response and remission rates among the 4 sub-groups found that the difference was not significant (response: $p = 0.103$; remission: $p = 0.366$).

3.3. Number of sessions and treatment days until response/remission

Table 3 presents the medians, 25th and 75th quartiles of number of sessions and number of treatment days required to reach response/remission. Overall, the median number of treatment sessions required to reach both response and remission was 28. The median of treatment days until response (remission) was 6 (8). With dosing of 3, 5 or 10 sessions/day, typically 3–4 treatment days lead to response and 4–5 days lead to remission.

3.4. Durability analysis

The number of responders who had assessments 60, 90, and 180 days after response are shown in Table 4, along with the percentages of patients who maintained the responder status throughout the period. The rates of durable response for 60, 90, and 180 days were 86.7%, 87.0% and 92.9%, respectively.

4. Discussion

This is the first naturalistic accelerated Deep TMS study which included 145 MDD patients. Accelerated Deep TMS led to 80% response and 51% remission rates in the whole dataset. These rates are comparable to the results of a recent large post-marketing study of non-accelerated Deep TMS (Tendler et al., 2023). Twice-daily sessions for on average 29 days led to 90% response and 56% remission. Three daily sessions for on average 8 days led to 75% response and 63% remission.

Table 2
Number of sessions, treatment days, remission, and response rates for the whole dataset and for various accelerated dosing.

Group	Whole dataset	Sessions Per Day 2x/day	3x/day	5x/day	10x/day
Total sessions, Mean (SD)	44.2 (20.7)	49.1 (23.4)	25.9 (21.5)	32 (16.8)	49.6 (11.0)
Treatment days, Mean (SD)	16.4 (14.7)	29.3 (13.4)	8.0 (6.8)	6.5 (3.5)	5.6 (2.0)
Sessions/day, Mean (SD)	4.7 (3.3)	1.73 (0.40)	3.3 (0.3)	5.2 (1.2)	9.1 (1.3)
Response (sample size)	80.2% (111)	89.6% (48)	75% (8)	81% (21)	67.6% (34)
Remission (sample size)	50.5% (111)	56.3% (48)	62.5% (8)	52.4% (21)	38.2% (34)

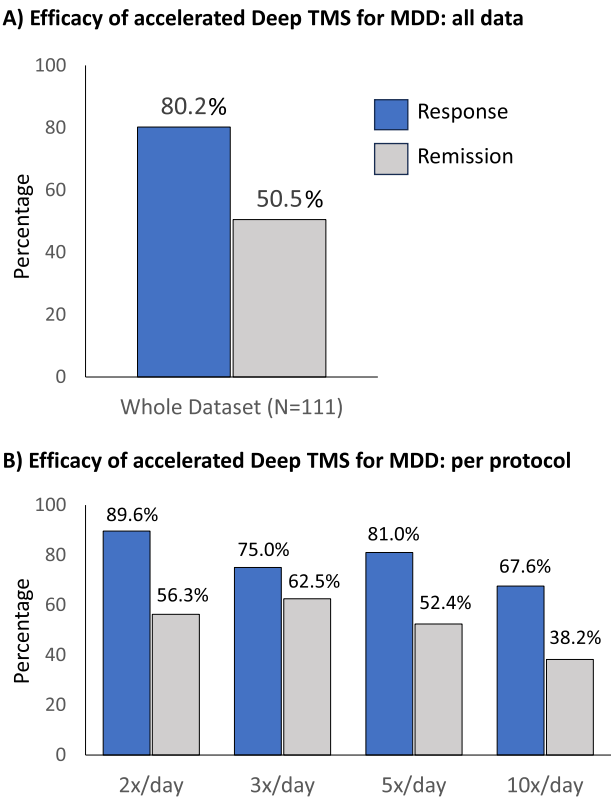

Fig. 1. Efficacy of accelerated Deep TMS protocols in patients with major depressive disorder (MDD). The data reflect response (blue/dark bars) and remission (gray/light bars) rates based on the most rated scale for the whole dataset (A) as well as the common protocols (B). The efficacy on average is similar to prior Phase IV data collection for standard 1x/day Deep TMS. There was no significant difference between the accelerated dosing protocols in this Phase IV study. More information on sample size can be found in Table 2.

Table 3
Medians and interquartile intervals of number of sessions and number of treatment days to reach response/remission for the whole dataset and for various accelerated dosing.

Scale	Time To Response (median, [interquartile interval]) Sessions	Treatment Days	Time To Remission (median, [Interquartile interval) Sessions	Treatment Days
Whole dataset	28 [16, 50]	6 [3, 17]	28 [17, 50]	8 [3, 25]
2 sessions/day	30 [16, 55]	17 [12, 28]	30 [21, 56]	26 [16, 35]
3 sessions/day	10 [10, 10]	3 [3, 5]	12 [10, 15]	4 [3, 4]
5 sessions/day	20 [16, 36]	4 [3, 8]	22 [17, 34]	4 [3, 10]
10 sessions/day	31 [22, 50]	4 [3, 5]	30 [28, 50]	5 [3, 5]

Table 4
Durability of response among patients that returned to the clinic for follow up visits after 60, 90 and 180 days.

Period	% Patients with a durable response	Number of Patients
60 days	86.7%	26 of 30
90 days	87.0%	20 of 23
180 days	92.9%	13 of 14

Five daily sessions for 6–7 days resulted in 81% response and 52% remission. Ten sessions/day for typically 5 days led to 68% response and 38% remission. Although the comparisons between groups were not significant, the observation that higher response and remission rates

were found following 3 or 5 daily Deep TMS sessions for 6–8 days than following 5 days of 10 daily sessions is interesting and worthy of further exploration. Prospective comparative studies with larger sample size are required to shed more light on the optimal dosing of accelerated Deep TMS for MDD.

It is instructive to compare the current results of accelerated Deep TMS with open label large, accelerated figure-8 TMS studies. In one study, 3 session/day of 10 Hz rTMS for 6 days led to 20.3% (23.7%) response rates based on HDRS (MADRS) in 58 patients (Fitzgerald et al., 2018). In a retrospective study, 20–30 sessions of 20 Hz applied 2 sessions/day led to 41.5% response and 35.4% remission in 65 patients, based on BDI (Schulze et al., 2018). In another retrospective study, 2 sessions/day for 20–30 days induced response in 45% of 73 patients based on MADRS (Desbeaumes Jodoin et al., 2019). A large, randomized study compared twice daily vs. once daily iTBS for 30 days (Blumberger et al., 2021). Among 103 patients who received twice-daily sessions, 44.3% reached response based on HDRS. A recent randomized study compared twice-daily and once-daily 10 Hz rTMS sessions in inpatients and found similar response/remission rates but shorter hospitalization period in the twice-daily group (Barnes et al., 2023). Among 109 patients who received on average 20 twice-daily sessions, response (remission) rates based on HDRS were 59.6% (44.9%). A large three-arm RCT (Randomized Controlled Trial) compared bilateral (right PFC cTBS and left PFC iTBS) 2–3 sessions/day with 80% or 120% rMT and a standard 10 Hz once daily rTMS. Response rates based on QIDS (Quick Inventory of Depressive Symptomatology) in the 80% (120%) rMT accelerated groups were 44.1% (36.8%) (Chen et al., 2021). The response/remission rates in the current Deep TMS study are higher than those reported in the studies using a figure-8 coil. This is especially remarkable since most of the above results were based on observer rating scales (HDRS or MADRS) while in the current work mostly patient self-report scales were available. Previous studies indicate that patients tend to self-classify as more severely depressed (O'Reardon et al., 2007; Zimmerman et al., 2012; Tendler et al., 2023). No head-to-head study comparing accelerated Deep TMS and figure-8 rTMS was done so far. A head-to-head study of non-accelerated TMS found significantly higher response rate with the H1 coil and a trend towards higher remission rate that did not reach significance (Filipčić et al., 2019).

Stanford Neuronavigation Therapy (SAINT) uses fMRI-guided 10 iTBS sessions/day for 5 days. High response and remission rates were found in an open label (Cole et al., 2020) and a sham-controlled study (Cole et al., 2022), although the sample sizes were small.

A previous study investigated 2 H1 Deep TMS sessions/day and found no significant difference between 10 and 15-days. 10-days led to 63% (38%) response (remission) rates compared to 83% (42%) in the 15-day group (Filipcic et al., 2021). These results are in line with the efficacy results in the current study.

Response and remission onset occurred on average after 28 sessions and 6–8 treatment days, namely 3–5 sessions per day. These are upper bounds since patients may have reached response/remission earlier than their scheduled assessment. In non-accelerated Deep TMS response/remission typically occurred after 16–17 treatment days (Tendler et al., 2023). Hence, accelerated treatments enables onset of response/remission after more sessions but less treatment days, making the point that it is not accelerated from a session's perspective but only from a day's perspective (like with SAINT). Twice-daily protocol does not induce a faster onset of response/remission. In contrast, with 3, 5 or 10 daily sessions, response/remission typically occurred after 3–5 treatment days. Similarly, the one-month response rate did not improve. This may be due to a ceiling effect for the H1, limitation in the rating scales which enquires about seven days, and the fact that this was real world study with other unknown variables.

Durability of response was remarkably high (87–93% maintained their responder status after 60–180 days), much higher than the durability found in Tendler et al. (2023) for non-accelerated Deep TMS (44–57%), though that was an underestimation due to patients not returning when they improve. Still the numbers of patients with durability data in this study and in the non-accelerated data set were low. Future larger scale studies will have to investigate if indeed accelerated Deep TMS leads to enhanced durability.

There are several limitations to this study. As an uncontrolled naturalistic study, placebo effect was not accounted for, and it may be amplified in patients who are investing to seek treatment schedules that are not reimbursed by insurance. Patients are paying out of pocket and spending a denser time in the clinic which may increase the expectation of improvement. Regarding provider bias, treatment sites were reimbursed for any line of data irrespective of the results, and providers were motivated to send as much data as they can. Hence there is no reason to believe there was a bias beyond their general desire for their patients to improve. As with all naturalistic studies, there was heterogeneity in the protocols given at the various sites that contributed data. Specifically, patients received between 2 and 10 daily sessions. Future studies must address the question of the optimal number of daily Deep TMS sessions and other parameters. Missing data influenced the durability results.

In conclusion, real-world use of accelerated Deep TMS with the H1 Coil for MDD offers resistant MDD patients a high probability to remit with rapid onset and lasting durability. Future randomized prospective studies should investigate the optimal dosing of accelerated Deep TMS for MDD including optimal number of daily sessions, overall number of sessions and the temporal distribution of treatment days.

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CRediT authorship contribution statement

Yiftach Roth: Writing – original draft, Formal analysis. **Colleen A Hanlon:** Writing – review & editing, Visualization. **Gaby Pell:** Validation. **Samuel Zibman:** Data curation, Software. **Tal Harmelech:** Project administration. **Owen S Muir:** Investigation. **Carlene MacMillan:** Investigation. **Tim Prestley:** Investigation. **David C Purselle:** Investigation. **Thomas Knightly:** Investigation. **Aron Tendler:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

YR, CH, GP are employed by and have a financial interest in BrainsWay. AT consults and has a financial interest in BrainsWay and commercial TMS. OSM and CM have a financial interest in Fermata, a commercial TMS center.

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