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Research paper

Alternate day dTMS combined with SSRIs for chronic treatment resistant depression: A prospective multicenter study

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ABSTRACT

Introduction: Chronic treatment resistant depression takes a substantial toll on patients' quality of life and alternative treatment options are limited. This prospective multicenter study evaluated the safety, tolerability and efficacy of four weeks of thrice-a-week deep transcranial magnetic stimulation (dTMS) in combination with selective serotonin reuptake inhibitors (SSRIs).

Methods: Forty patients who failed to respond during a 16-week double-blind placebo controlled (DBPC) trial of dTMS or sham dTMS as monotherapy were screened and started a treatment of previously tolerable but ineffective SSRI. After ten days of medication, high frequency dTMS was added three times a week for four weeks.

Results: dTMS combined with SSRIs was well tolerated, with only headaches as a related adverse event ($n = 4$), which did not cause drop outs. Six patients were excluded from analysis: 1 was missing screening data and 5 received less than 10 sessions. Out of 34 patients included in this study, 12 (35.3%) patients remitted (HDRS-21 < 10). No significant differences were found between patients who had received sham or active dTMS in the earlier DBPC multicenter trial.

Limitations: This was a small scale open study of dTMS with SSRIs in patients that failed to respond during a DBPC dTMS trial, although a carryover effect cannot be excluded. Comparative efficacy of dTMS with and without SSRIs and specific dosing and protocol parameters warrant specifically-designed large-scale controlled studies.

Conclusions: Thrice weekly dTMS at 120% motor threshold(MT), 10 HZ, 3-s trains, 20-s intervals, 2400 daily pulses, can augment formerly ineffective SSRI treatment.

1. Introduction

Major depressive disorder (MDD) is a common, chronic condition with high rates of morbidity and disability (Lopez et al., 2006). The most challenging subgroup are those with treatment resistant depression (TRD), particularly patients who did not respond to two or more medications, as there is a dramatic decline in the efficacy of subsequent medication trials (Rush et al., 2006b). Treatments with proven efficacy for TRD include electroconvulsive therapy (ECT), augmentation of antidepressants with antipsychotics, daily (5 sessions per week) transcranial magnetic stimulation (TMS) or deep TMS (dTMS). However, these methods include drawbacks such as the need for anesthesia (ECT), high rates of metabolic and other side effects augmentation drugs (Ressler and Mayberg, 2007), or might be burdensome for some patients (TMS) (Conway et al., 2017). One alternative option that has not yet been studied is less frequent deep TMS sessions (<5 per week) as an augmentation to antidepressants. We chose to offer this option to patients who completed the entire 16-week treatment in the double-blind placebo controlled (DBPC) multicenter study of deep TMS (dTMS) for TRD (Levkovitz et al., 2015), but failed to respond. In the DBPC study, the dTMS monotherapy included 20 sessions over 4 weeks (5/week) followed by 24 sessions over the next 12 weeks (2/week). At week 5, response (38.4%) and remission (32.6%) rates were significantly higher in the dTMS than in sham group (21.4% and 14.6%, respectively).

In the current open multi-center prospective trial we combined three-a-week dTMS with SSRI medications. The study goals were to inform the safety and efficacy of this approach, which is more characteristic of real-life practice, where patients may not be able to come in five days a week and are more likely to remain on their antidepressants than discontinue them. It was also informative on the safety of using a

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longer stimulation train (3 s of 10 Hz) than in the DBPC (2 s of 20 Hz). Offering this open label study for nonresponders who completed the sixteen week DBPC was helpful during the recruitment process of the DBPC study where the chances for randomization to the sham arm were 50%, as well as in maintaining patients in the earlier DBPC study.

2. Methods

2.1. Study overview

The study was conducted at 10 research sites, 7 in the US and 3 in Israel. 68% of the patients were from the US and 32% of the patients were from Israel. The study was approved by the respective institutional review boards and all patients signed informed consents. The clinicaltrials.gov identifier was NCT01361815. Study centers included Advanced Mental Health Care Inc. (Palm Beach, FL, USA), Beer Yaacov Mental Health Center (Beer Yaakov, Israel), Greater Nashua Mental Health Center (Nashua, NH, USA), Senior Adults Specialty Research (Austin, TX, USA), Hadassah Medical Center (Ein-Karem, Jerusalem, Israel), McLean Hospital (Belmont, MA, USA), Johns Hopkins University (Baltimore, MD, USA), University of Texas SW Medical Center (Dallas, TX, USA), UC Davis Center for Mind & Brain (Sacramento, CA, USA), Shalvata Mental Health Center (Hod Hasharon, Israel).

2.2. Subjects

The patient population included outpatients 22–68-years-old (following the inclusion criteria of the earlier DBPC trial) who suffered from major depressive disorder according to the Structured Clinical Interview (SCID) for DSM IV. Patients already completed the DBPC MDD dTMS study (from both dTMS and sham dTMS arms, see Table 1) without reaching response (defined as ≥50% improvement on the Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960) score compared to baseline).

Inclusion criteria included an HDRS-21 score at screening ≥16, as a cutoff for relapse(Kennedy, 2002); the duration of the current depressive episode of at least 22 weeks but no more than 7.5 years, and patients must have failed between 1–4 medications and the dTMS DBPC clinical trial in the current episode.

Exclusion criteria included patients who discontinued the DBPC MDD study for tolerability, safety or compliance issues, current psychosis, allergy to SSRIs, pregnancy, women capable of pregnancy who were unwilling to use birth control and current suicidality (HDRS-21 item 3 score of 3 or 4).

2.3. Study design

This was a four-week study of H1-dTMS treatments administered three times a week while patients were on SSRI medications. Patients were recruited within four weeks of their final DBPC dTMS treatment, which was a monotherapy. Eligible patients were treated with SSRIs, starting ten days before their first dTMS treatment. The SSRIs that were selected were medications types approved by the FDA for MDD in doses that patients had previously tolerated, despite a lack or loss of efficacy.

Table 1
Demographics of the participants in the current study.

	% female	Age	% Caucasian	ATHF	# meds at highest ATHF
Sham in pivotal study	62.5	47.65	87.5	3.563	1.125
Active in pivotal study	55.556	48.7	94.444	3.389	1.22

ATHF- Antidepressant Treatment History Form.

Subjects were discontinued from the study at any point if they were considered by the investigators to be at an elevated risk for suicide.

2.4. Medications

The following medications and dosages were included: Citalopram 20–40 mg/day, Escitalopram 10–20 mg/day, Fluoxetine 20–40 mg/day, Paroxetine 20–40 mg/day, or Sertraline 50–200 mg/day. Dosage of SSRI medications could be adjusted (within the above ranges) during the study if side effects developed. Insomnia medications were allowed, up-to an equivalent of 3 mg of Lorazepam. No other psychotropic medications were allowed.

2.5. dTMS protocol

The TMS operator determined the patient's resting motor threshold (MT) at baseline and then re-checked it before every treatment according to a previously described method (Levkovitz et al., 2009). Treatments were administered three non-consecutive days per week over the prefrontal cortex, using the H1 coil developed for deeper and non-focal stimulation of structures in the dorsolateral, ventrolateral and medial prefrontal cortex, areas that have been suggested to be particularly relevant for therapeutic effects of non-invasive brain stimulation In MDD (Fitzgerald et al., 2003). The coil was placed 6 cm anterior to the right hand “hot spot” (Levkovitz et al., 2009). dTMS treatments were administered at 120% of MT, 10 Hz, 3-s pulse train, 20-s intertrain interval, 80 trains, totaling 2400 pulses over 30.6 min per session. dTMS treatment intensity could be increased over three sessions: in the first session the patient had to tolerate 100%MT, in the second 110% MT, and from the third session onwards the patient had to be receiving 120%MT. Patients wore hearing protection. During each dTMS treatment session patients were asked by the operator about adverse events and changes in their medications or medical conditions.

2.6. Efficacy and safety assessments

Patients were evaluated for HDRS-21, Clinical Global Impressions scale-severity (CGI-S) (Guy, 1976), quick inventory of depressive symptoms (QIDS-SR) (Rush et al., 2006a; Trivedi et al., 2004) at screening (day −10), baseline (day 0), after 2 weeks (day 14) and 4 weeks (day 28) of dTMS treatment. Baseline evaluations included physical examination (including vitals, height and weight), neurological examination, mental status examination, HDRS-21, clinical global impression scale - severity (CGI-S), quick inventory of depressive symptoms (QIDS-SR), scale for suicidal ideation (SSI) (Beck et al., 1979), Young mania rating scale (YMRS) (Young et al., 1978), mini mental status examination (MMSE) (Folstein et al., 1975). All the raters were required to pass a certification program to ascertain interrater reliability. The primary endpoints were safety and tolerability. Safety was determined by the incidence of adverse events, vital signs, physical and neurological examinations, mania on the YMRS and suicidality on the SSI. Tolerability was defined by the number of subjects who discontinued due to adverse events. Efficacy was evaluated by measuring changes from baseline to the end of week 4 in the HDRS. In addition changes in QIDS and CGI-S were evaluated, and remission defined as HDRS-21 < 10 at the end of week 4, response defined as at least a 50% decrease in HDRS-21 score at the end of week 4 compared to baseline are reported, and every item on the HDRS-21 counts toward the total score (Levkovitz et al., 2015; Kishi et al., 2017; Berlim et al., 2014a; Harel et al., 2014; Herwig et al., 2007; Kreuzer et al., 2015; Prasser et al., 2015; Stern et al., 2007).

2.7. Statistical analysis

Since sample size at each research site was small, no difference could be observed between the sites, and data from all sites were

combined. All data are presented as mean ± SEM. The data was tested for normality using Shapiro–Wilk test (Shapiro and Wilk, 1965) and for sphericity using Mauchly sphericity test (Mauchly, 1940). HDRS and QIDS data was normally distributed and sphericity is not violated and were analyzed by parametric tests. Specifically, the changes in between multiple time points were determined by one-way repeated measures analysis of variance (ANOVA) with time as within-subject factor, followed by Fisher's least significant difference post hoc test. CGI-S data was not normally distributed and spheric and was analyzed by non-parametric tests. Specifically, the changes between multiple time points were assessed by Friedman test, followed by Wilcoxon post hoc test. The change in safety measures between baseline and 4 weeks was assessed by paired *t*-test. A significance level (α) of $p < 0.05$ was set for all statistical analyses. All data analysis were conducted with Statistica 8.0 (StatSoft, Inc., USA).

3. Results

3.1. Subjects

Of the 45 patients that were screened, 40 patients met inclusion criteria of HDRS ≥ 16 at screening and received dTMS treatment. Out of 40 patients 1 was missing screening data and 5 received less than the required minimum of 10 treatment sessions. The remaining 34 (16 received sham and 18 received verum stimulation in the earlier DBPC study) met the inclusion criteria and are included in the efficacy analysis (mean age of 47.1 (ranging from 23 to 68 years old), 41.2% male, and 91.2% Caucasian). Their baseline mean HDRS-21 was 19.2 (SEM = 0.96), mean QIDS 16.7 (SEM = 1.11), and mean CGI-S 4.4 (SEM = 0.15).

3.2. Safety measures

Comparing baseline to 4 weeks, the mean weight decreased significantly by 0.77 kg (ranging from −2 to +5.6 kg; SEM = 0.29, $p = 0.01$). There were no changes in temperature and blood pressure. There were no significant changes in the physical examination, neurological examination, YMRS and SSI. The MT varied during individual treatment by an average of +/− 4.3% (SEM +0.5%/−0.4%) with maximal change of 9.8%.

3.3. Tolerability measures

The only adverse event most probably related to the device was headache during or after treatment. It was reported by four patients, but none resulted in treatment discontinuation.

3.4. Efficacy measures

HDRS. One-way repeated-measures ANOVA with treatment stage as a within subject factor revealed a significant main effect ($F(2, 33) = 20.85$; $p < 0.001$), and post hoc analysis showed that both 2 ($p < 0.001$) and 4 ($p < 0.001$) weeks were significantly lower than baseline. No significant difference was found between 2 and 4 weeks of treatment (Fig. 1). Response and remission rates were 35.3% (12 out of 34; Table 2). Eleven out of 34 both responded and remitted, while 1 out of 34 responded but did not remitt and another 1 out of 34 remitted but did not respond as the baseline HDRS for this patient was 17 and at week 4 the HDRS dropped only to 9. There was no difference between response and remission rates in patients who in the DBPC received verum or sham dTMS.

QIDS. Findings mirrored HDRS: one-way repeated-measures ANOVA with treatment stage as a within subject factor revealed a significant main effect ($F(2, 31) = 13.46$; $p < 0.001$), and post hoc analysis showed that both 2 ($p < 0.001$) and 4 ($p < 0.001$) week scores were significantly lower than baseline. No significant difference was found between 2 and 4 weeks of treatment (Fig. 2).

CGI-S. One-way repeated-measures ANOVA with treatment stage as a within subject factor revealed a significant main effect ($F(2, 34) = 37.62$; $p < 0.001$), and post hoc analysis showed that both 2 ($p < 0.001$) and 4 ($p < 0.001$) weeks were significantly lower than baseline and 4 weeks was significantly lower than 2 ($p = 0.002$) weeks (Fig. 3). The number of responders (CGI-S ≤ 2) steadily increased from 0% at baseline, to 20.5% (7 out of 34) and 38.2% (13 out of 34) after 2 and 4 weeks of treatment, respectively.

4. Discussion

This open label study indicates that alternate day 10 Hz dTMS combined with SSRI treatment for is a safe an efficacious option for chronic TRD. The treatment protocol of the present study produced 35.3% response and remission rates in this clinically challenging population with minimal side effects. The clinical efficacy profile is consistent with existing published dTMS data (Isserles et al., 2011; Levkovitz et al., 2007, 2009, 2011, 2015). A recent meta-analysis of 11 dTMS studies in MDD found pooled remission and response rates of 29% and 62%, respectively, similar to prior publications from the same group (Gellersen, 2017; Kedzior et al., 2017, 2015). The current study demonstrated that comparable rates can be achieved even in patients who just failed to respond to a previous dTMS treatment. The present results can be compared to the results of a former study (Harel et al., 2011), where patients received dTMS five days a week for four weeks, twice a week for eight weeks, then once a week for ten weeks. Between weeks 4 and 22, the probability of response and remission increased from 46.2% to 81.12% and from 26.92% to 71.45%, respectively. Similarly, analysis of the dTMS DBPC multicenter trial demonstrated that among the group of patients who did not reach response during the 4 weeks of acute active dTMS treatment and nevertheless continued for bi-weekly treatments over 12 weeks, most of them reached response (72.7%) and remission (63.6%) (Yip et al., 2017). Therefore, accumulating evidence suggests that MDD patients who did not reach response after 4 weeks of acute dTMS treatment benefit from a continuation treatment at lower frequency of weekly sessions.

The 35.3% response rate of this open label pulse open label study is comparable to the results of a recent study where non-responders to left high frequency conventional rTMS were randomized to an additional three weeks of 10 Hz left treatment or low frequency right sided or sequential bilateral treatment with a resulting 36% overall response rate and no significant difference between the arms (Fitzgerald et al., 2018a). It is also similar to the results of the non inferiority study of MRI guided conventional rTMS to the left DLPFC where both 37.5 min of 10 Hz and the 3 min iTBS group had ~30% remission after six weeks of daily treatment (Blumberger et al., 2018). Given the resistance level of patients in the current study (which were already medication resistant to be eligible for the earlier DBPC phase, and did not respond to active or sham dTMS provided daily over 4 weeks and then bi-weekly over additional 12 weeks), the effectiveness of 10 Hz dTMS in just 3 sessions per week over 4 weeks, is remarkable.

This study's schedule was similar to a pilot study of dTMS combined with a traumatic script in the treatment of chronic post traumatic stress disorder. In that study, patients were treated over the medial prefrontal cortex three times a week for four weeks, and the combined active dTMS with provocation had a significant treatment effect evident by a reduction in the CAPS (Isserles et al., 2013).

Interestingly, in the present study, the clinical outcome was almost similar between patients who earlier in the DBPC study received active dTMS and those who received sham dTMS. The slightly increased response rate among patients who earlier received and did not respond to active dTMS (27% vs. 43% in the previously sham treatment group) might indicate that this group was more treatment resistant. Yet, the differences between those groups might be partially due to variability in the concurrent SSRI medications or doses. On the other hand, among

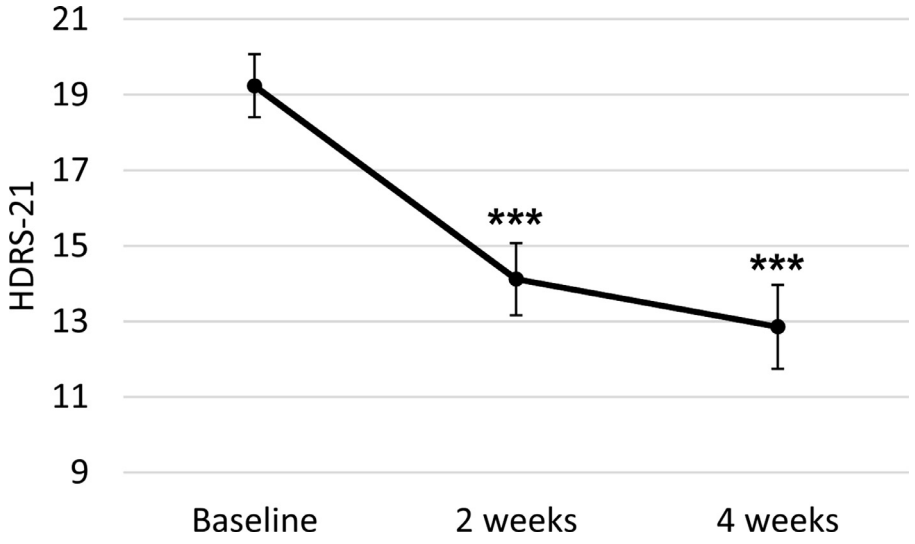

Fig. 1. Effect of dTMS with SSRI on HDRS-21 at baseline, 2 and 4 weeks after start of the treatment. Data are presented as mean +/− SEM. *** $p < 0.001$ as compared to the baseline.

Table 2
Remission and response at the end of the current study in patients who received dTMS or Sham in the pivotal DBPC study.

	Total		Treatment received – pivotal DBPC study			
			Previous dTMS		Previous sham	
	N	%	N	%	N	%
Remission	12 of 34	35.3	6 of 18	33.3333333	6 out 16	37.5
Response	12 of 34	35.3	5 of 18	27.7777778	7 out 16	43.75

DBPC- double blind placebo-controlled.

the patients who received dTMS treatment in the earlier DBPC study, the additional four weeks could be the time necessary to reach response or remission, or that the SSRIs combined with a 10 Hz (rather than 20 Hz, see below) dTMS treatment, resulted in remission that was not achieved earlier. It is possible that chronic TRD patients gain more from 90,000 pulses over ninety days than over three days. Even though several approaches are being tested to accelerate the effects of TMS through the use of multiple sessions of high frequency or theta burst on a daily basis, the compared population is not the subset that failed conventional treatment (Dardenne et al., 2018; Duprat et al., 2016; Fitzgerald et al., 2018b; McGirr et al., 2015; Schulze et al., 2018). Another plausible explanation for the response and remission achieved in the previously active dTMS group is that the open phase of the present study employed stimulation parameters that were more effective at least for these TRD patients (10 Hz for 3 s with total of 2400 pulses/session compared to 18 Hz for 2 s with a total of 1980 pulses/session). Even though TMS devices have been commercially available for many years, many practical questions about the optimal protocol for the treatment of TRD remain unknown. Almost any of the variables in the treatment can be modified: the number of pulses, number of treatments per day, frequency of the pulses, train duration, inter train interval (Cash et al., 2017), intensity, location, cognitive state during treatment (Isserles et al., 2011) and medication status, all of which may be varied between individuals. To date, there is no conclusive proof that 20 (or 18) HZ is better or worse than 10 HZ for depression (DeBlasio and Tendler, 2012).

The variability in motor thresholds suggests that MTs may need to be checked more frequently in patients on medications, since

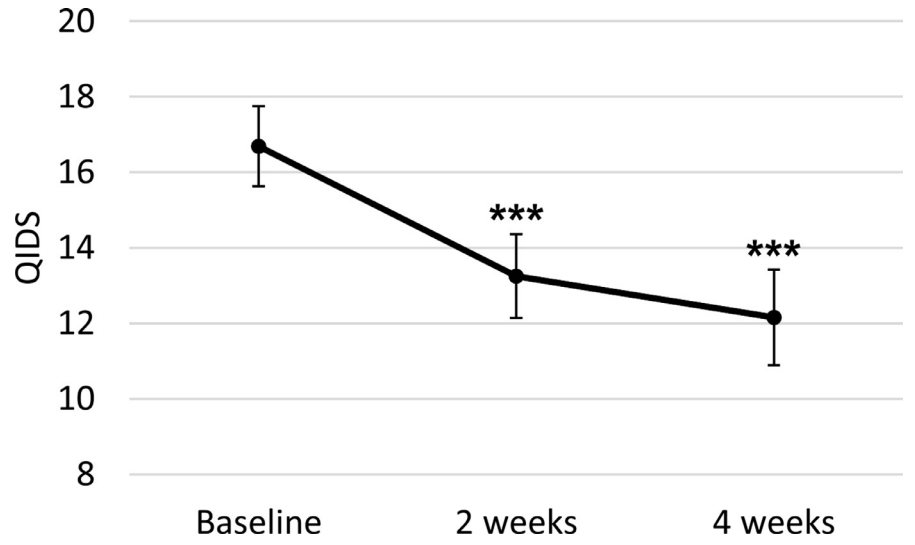

Fig. 2. Effect of dTMS with SSRI on QIDS at baseline, 2 and 4 weeks after start of the treatment. Data are presented as mean +/− SEM. *** $p < 0.001$ as compared to the baseline.

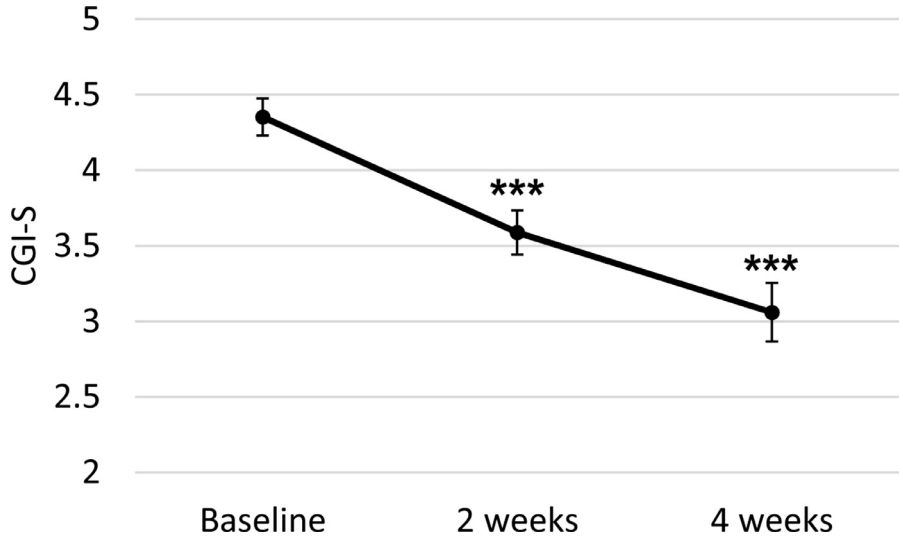

Fig. 3. Effect of dTMS with SSRI on CGI-S at baseline, 2 and 4 weeks after start of the treatment. Data are presented as mean +/− SEM. *** $p < 0.001$ as compared to the baseline.

erroneously low treatment intensity may result in reduced treatment efficacy, while excessively high intensities may increase the risk of adverse events such as application site pain and seizures. The slight weight loss observed in the present study, although not found to be significant in earlier dTMS studies in MDD populations, is promising particularly for patients who frequently discontinue antidepressant treatments because of a side effect of weight gain. This finding needs to be confirmed in a larger cohort of patients on medications with TMS.

The literature is not consistent regarding remission cutoffs using the HDRS-21. Remission rates are often calculated based on HDRS-17, using ≤7 as cutoff, where 4 of the 21 items are not counted for the total score, and merely used for noting the subtype of depression and changes in related symptoms. Some studies used all of the items on the HDRS-21 and <10 as cutoff (Berlim et al., 2014a; Harel et al., 2014; Kishi et al., 2017). Some studies have even used a cutoff of 12 for remission, while others propose a cutoff of <5 (Sawamura et al., 2018; Zimmerman et al., 2012, 2005). In this continuation study we used all 21 items on the HDRS-21 with a remission cutoff of <10 to allow some basis for comparison between the current results and remission rates in the original DBPC multicenter study, we used the same definition for remission. Additionally, these were cutoff criteria that were acceptable by the FDA who were regulating this study.

5. Limitations

This was a small scale open study of dTMS combined with SSRIs in patients that failed to respond during a DBPC dTMS trial. Therefore, a larger scale, double-blind study is necessary to further test the efficacy of this 10 Hz 3 weekly dTMS sessions treatment protocol. Moreover, a carryover effect of the DBPC dTMS trial cannot be excluded.

This study was not designed to test whether dTMS with medications is more efficacious than monotherapy dTMS for treatment resistant depression. To answer such a question, an appropriately powered multi arm study, preferably using a specific medication would be required. Such study would include-: active TMS with medication, active TMS with placebo medication, sham TMS with medication, sham TMS with placebo medication. There have been no such studies, and there is no clinical or preclinical evidence to demonstrate a synergistic or even additive effect of TMS with medications (Berlim et al., 2013; Berlim et al., 2014b).

Nevertheless, most clinicians believe that there is benefit in combining treatment modalities. Indeed, a recent study found that a few TRD patients' condition worsened after being taken off medications they have not responded to, during a wash out period before a clinical trial (Lapidus et al., 2014). Finally, an appropriately powered blinded study between the 18 Hz protocol of the DBPC study and the 10 Hz protocol of the present study is necessary to answer whether one frequency is more effective than the other.

To summarize, we show for the first time that four weeks of thrice weekly dTMS combined with SSRIs is a safe, tolerable and effective treatment for patients with long standing treatment resistant depression. The efficacy of less frequent treatments is novel, and promising to patients who cannot come in on a daily basis, but this should be examined in larger sham controlled or comparative studies.

Author statement

Contributors

Aron Tendler: Site investigator at Advanced Mental Health Care Inc., Manuscript preparation and corresponding author.
Roman Gersner: Statistical analysis and figure preparation.
Yiftach Roth: Study design and manuscript review.
Abraham Zangen: Study design and manuscript review.

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Brainsway Ltd. provided the TMS equipment, paid the clinical trial sites to administer the treatments, and gave the patients a small amount of money to cover travel expenses.

IRB

As stated in the manuscript, every site had IRB approval. The commercial IRB was Sterling IRB. Academic institutions had their own IRB.

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Declaration of interest

Drs. Tendler, Gersner, Roth and Zangen have a financial interest in Brainsway.

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