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Effectiveness of a second deep TMS in depression: A brief report

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ABSTRACT

Objectives: Deep transcranial magnetic stimulation (DTMS) is an emerging and promising treatment for major depression. In our study, we explored the effectiveness of a second antidepressant course of deep TMS in major depression. We enrolled eight patients who had previously responded well to DTMS but relapsed within 1 year in order to evaluate whether a second course of DTMS would still be effective.
Methods: Eight depressive patients who relapsed after a previous successful deep TMS course expressed their wish to be treated again. Upon their request, they were recruited and treated with 20 daily sessions of DTMS at 20 Hz using the Brainsway's H1 coil. The Hamilton depression rating scale (HDRS), Hamilton anxiety rating scale (HARS) and the Beck depression inventory (BDI) were used weekly to evaluate the response to treatment.
Results: Similar to the results obtained in the first course of treatment, the second course of treatment (after relapse) induced significant reductions in HDRS, HARS and BDI scores, compared to the ratings measured prior to treatment. The magnitude of response in the second course was smaller relative to that obtained in the first course of treatment.
Conclusions: Our results suggest that depressive patients who previously responded well to deep TMS treatment are likely to respond again. However, the slight reduction in the magnitude of the response in the second treatment raises the question of whether tolerance or resistance to this treatment may eventually develop.

1. Introduction

The partial effectiveness of pharmacotherapy in the treatment of major depressive disorder (MDD) on the one hand, and the major side effects of ECT on the other hand, called for the development and study of novel brain stimulation techniques. These techniques are attempted to overcome treatment-resistant depression. Repetitive transcranial magnetic stimulation (rTMS) is a relatively new brain stimulation technique, and has already been proven effective in treatment for major depression (Kozel and George, 2002; Loo and Mitchell, 2005; O'Reardon et al., 2007; Jorge et al., 2008). Recently, to improve the magnitude and rate of the antidepressant effect of TMS, a novel coil allowing stimulation of deeper brain regions was developed. This coil is termed the H-coil. The effectiveness of deep TMS in the treatment of depression has been demonstrated in four published studies so far: a medium size study which enrolled sixty five patients (Levkovitz et al., 2009), a medium size study which enrolled fifty seven patients (Isserles et al., 2010), a case series of seven patients (Rosenberg et al., 2010), and with a lower response rate in a series of depressive patients treated previously with electroconvulsive treatment (Rosenberg et al., 2010). A comprehensive safety study performed in healthy volunteers showed the safety of H-coils used even in high frequencies and intensities (Levkovitz et al., 2007). One case of DTMS-induced seizure has been reported in a patient receiving high doses of several antidepressant drugs (Isserles et al., 2010) and two more cases of seizures occurred in ongoing DTMS studies (personal communication), in which patients were receiving psychiatric medications that increase the risk for seizures. Out of 135 MDD patients that have participated in DTMS studies for the treatment of MDD, 32 (25%) patients reported the following side effects: minor headaches (28 patients) (Levkovitz et al., 2009; Isserles et al., 2010), dizziness and nausea (one patient) (Rosenberg et al., 2010), numbness of the right temporal and right cervical zone (one patient) (Rosenberg et al., 2010), insomnia (one patient) (Rosenberg et al., 2010), and foul smell and bad taste (one patient) (Rosenberg et al., 2010). Overall, despite the fact that 1 of 4

Abbreviations: TMS, Transcranial magnetic stimulation; MDD, major depressive disorder; rTMS, repetitive TMS; TRD, Treatment resistant depression.

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patients experienced side effects, the treatment proved to be tolerable, and most of the patients suffered no side-effects, nor complained of any significant discomfort (Isserles et al., 2010). The Isserles et al. study reported that a few patients complained of mild and transient headaches, typically during the first week, without any treatment or with common analgesics (Isserles et al., 2010).

Repeated TMS courses using standard TMS coils were shown to be effective in patients with refractory depression (Demirtas-Tatlidede et al., 2008; Fitzgerald et al., 2006; Pinhas, 2003). Clinical benefits were sustained for up to five months (Demirtas-Tatlidede et al., 2008).

In this study, we report the effectiveness of a second course of deep transcranial magnetic stimulation in the treatment of major depression.

2. Methods

We used Brainsway's H1 coil as reported (Levkovitz et al., 2007, 2009; Rosenberg et al., 2010). The most effective electric field produced by the coil is oriented in an anterior–posterior axis, with hemispheric preference for the left hemisphere.

The first step in the procedure is to locate the "hot-spot" on the patient's scalp, i.e., the point in which minimum magnetic field will cause a motor response in the form of twitching of the contra-lateral finger muscles in the hand. After locating the "hot-spot" we advance the coil 5.5 cm in a line parallel to the sagittal suture of the skull. Patients were treated at 120% of the motor threshold. Each train of pulses included 40 pulses within 2 s (20 Hz). 42 trains were given adding up to 1680 pulses per treatment session with inter-train interval of 20 s. Patients underwent 5 courses per week for 4 weeks. The stimulation parameters are identical to those that the patients received in their previous course of DTMS treatment.

Patients signed an informed consent form approved by the Israeli Ministry of Health and the local IRB. Patients were also evaluated with the Hamilton depression rating scale (HDRS-24), the Hamilton anxiety scale (HAS) and the Beck depression inventory (BDI) at baseline and weekly thereafter, following their 5th, 10th, 15th and 20th daily treatment.

We considered treatment response to be a reduction in HDRS-24 of at least 50%, and remission to be a reduction of the score to 10 or below (Frank et al., 1991).

2.1. Subjects

We enrolled eight patients — four females and four males. All of these patients suffer from major depression according to the DSM-IV-TR criteria, and no one had responded to at least two adequate antidepressant trials in terms of dosage and duration. The mean age was 47 (SD = ±9.8). Mean age of first depressive episode was 27 (SD = ±17.5). The mean time for depression relapse after the first treatment was 4 (SD = ±4.2) months. During the first treatment four of the eight patients were antidepressant free; one patient was being treated with Clomipramine, and another patient with Duloxetine and nortryptyline. The third patient was on Mianserin (a tetracyclic compound) and the fourth was treated with Escitalopram. During the second treatment session, four of the patients were antidepressant-free and the rest were treated as follows: one with Trazodone, reboxetine and escitalopram, the second patient with duloxetine and nortryptyline, the third with duloxetine and mianserine and the fourth with venlafaxine and valproic acid. One subject underwent a course of ECT with partial remission before the first course of treatment using deep TMS (Table 1).

Table 2
First treatment table of results.

	Baseline	After 20
HDRS mean ± SD	28.8 ± 3.8	9.8 ± 4
HDRS ANOVA P value		<0.0001
HDRS F value		32.5
HDRS Lambda		130
HARS mean ± SD	19.1 ± 5.5	7.3 ± 2.8
HARS ANOVA P value		<0.0001
HARS F value		18.2
HARS Lambda		73.1
BDI mean ± SD	25.1 ± 5.8	8 ± 4.4
BDI ANOVA P value		<0.0001
BDI F value		14.2
BDI Lambda		57.1

3. Clinical evaluations and results

3.1. First treatment

Results of the first treatment are presented in Table 2.

3.2. Second treatment

Results of the second treatment are presented in Table 3.

3.3. Comparison between results of first and second courses

In the second course of deep TMS, the HDRS, HARS and BDI results were improved significantly compared to the baseline ratings (measured just prior to the second treatment). However, the

Table 1
Demographic data.

Age	Antidepressant medication during second treatment	Antidepressants during first treatment	Length of response after first treatment (months)	Number of depressive episodes	Family history of depression	Length of depressive episode prior to the first treatment (months)	Age of depressive disorder onset	Prior ECT courses	Education (years)
55	Trazodil, Reboxetine, Escitalopram	Bondormin, Cadex	11	1	No	24	53	None	11
48	Venlafaxine, Valpromide	Clomipramine	6	1	No	4	46	None	18
58	No medication	No medication	1	Many, not assessed	No	6	12	None	15
37	No medication	No medication	0.5	1	Father	180	22	None	15
57	No medication	Cipralex	2	1	No	9	3	None	20
32	Duloxetine, Nortryptylin	Cymbalta, Nortyline	0.5	0	Cousin	72	26	None	15
39	Duloxetine, Mianserin	Mianserin	2	3	No	4	9	1	Religion, not assessed
47	No medication	No medication	9.5	Many, not assessed	No	2	43	None	15

Table 3
Second treatment table of results.

	Baseline	After 5	After 10	After 15	After 20
HDRS mean ± SD	26.3 ± 3.2	19.7 ± 6	16 ± 4.7	15.1 ± 4.6	13.1 ± 5.5
HDRS ANOVA P value			0.0009	>0.0001	>0.0001
HDRS F value			11.9	11.8	14
HDRS Lambda			23.9	35.5	56.1
HARS mean ± SD	22.7 ± 6.4	15 ± 5.8	12.6 ± 6.8	12.2 ± 5.9	11 ± 5.6
HARS ANOVA P value			0.0018	>0.0001	>0.0001
HARS F value			10.3	12.3	12.2
HARS Lambda			20.6	36.9	49
BDI mean ± SD	23.5 ± 7.3	20 ± 8.6	16.2 ± 6.7	14.8 ± 7.5	15 ± 6.6
BDI ANOVA P value			0.17	0.056	0.033
BDI F value			2	2.9	3
BDI Lambda			4	8.8	12.2

improvement was not as substantial as in the first treatment sessions. After the first course, the average improvement of HDRS was 64.1% compared to only 50.7% after the second course. The average improvement of HARS was 59.7% in the first course, compared to only 47.5% after the second course; mean BDI improved by 67.7% in the first course compared to only 25.8% after the second course (see Table 2).

A significant difference was observed between the average improvement in percentages of HDRS in the first and the second treatment ($p = 0.013$, paired t-test). In addition, a significant difference was observed between the average improvement in percentages of BDI in the first and the second treatment ($p = 0.018$, paired t-test).

3.4. Side effects

One patient reported dizziness during the last ten sessions of the first treatment. This dizziness was self-limited and caused no falls and/or injuries.

4. Discussion

High relapse rates in severe MDD patients are one of the great burdens of this disease (Dannon et al., 2002). Naturalistic studies show that the relapse rate during the 6 to 12 months following ECT exceeds 50% (Sackeim et al., 2001).

Dannon et al. reported that the relapse rates in MDD patients treated with either rTMS or ECT were similar and close to 25% (rather than 50%) for 6 months after the treatment (Dannon et al., 2002). In a multicenter, randomized, parallel design, 6-month trial, two hundred patients with unipolar depression who had remitted with a course of bilateral ECT were randomly assigned into two treatment groups receiving either continuation ECT or continuation pharmacotherapy for six months. 37.1% of patients receiving ECT and 31.6% of patients receiving pharmacotherapy experienced relapse (Kellner et al., 2006). In another study including 159 patients, Sackeim et al. reported that the continuation of pharmacotherapy with nortriptyline hydrochloride or a combination of nortriptyline and lithium carbonate could prevent post-ECT relapse (Sackeim et al., 2001). Over the 24-week trial, the relapse rate for a placebo was 84%, for nortriptyline was 60% and for the nortriptyline-lithium combination was only 39%. The authors concluded that with pharmacological treatment all remitted patients experienced relapse within 6 months of stopping ECT (Sackeim et al., 2001). The high relapse rates of MDD necessitate reproducible treatment strategies, one of the possibilities is repeated transcranial magnetic stimulation.

Demirtas-Tatlidede et al. reported an effective second antidepressant course of rTMS (using a standard figure-eight coil) in 16 medication-free patients with refractory MDD that initially had clinically significant antidepressant responses to a 10-day course of 10-Hz rTMS. Patients were followed for four years. In this patient group, despite the lack of adjuvant antidepressant medication, the mean interval between treatment courses was approximately five months. The medication-free period ranged from 26 to 43 months. Repeated daily sessions of rTMS have demonstrated an effective second antidepressant course effect in patients with refractory depression who initially showed a clinically significant benefit. The duration of effect varied across patients, but benefits were sustained for a mean of nearly five months (Demirtas-Tatlidede et al., 2008). Fitzgerald et al. reported an effective second antidepressant course in six of seven patients treated with high frequency rTMS to the left prefrontal cortex. Three of the six patients responded fully while three responded partially in the second course. One patient did not respond to the second course of rTMS (Fitzgerald et al., 2006). The present study is the first study to report at least a partially effective second antidepressant course using the H-coil deep TMS system. Almost all patients responded to the second course of the DTMS treatment however, our results may also imply some development of tolerance to the DTMS treatment. The difference in the baseline scores before the second treatment may also explain the reduced efficacy after the second treatment. Finally, it is important to note that these patients are a sub-population of MDD patients that responded to the first DTMS treatment, but underwent relapse within 4 ($SD = \pm 4.2$) months, and may not represent the population of *all* patients that responded to the first DTMS treatment.

Evolvement of tolerance/resistance of depression to DTMS cannot be concluded from our study on account of the small sample of patient's size, even though the statistically significant change in the average percentage of HDRS improvement after the second treatment course supports this possibility. In addition, it is important to note that the study design prevents ruling out a possible placebo effect and expectancy bias, or the possibility of improvement having been the result of other factors, such as the natural course of the illness. This statement is true in regard to both first as well as second courses of Deep TMS.

At the most recent follow-up two of the eight patients relapsed. In addition to the question whether deep TMS will be found to be less effective with each additional relapse, another question that remains to be answered is whether deep TMS may be able to serve as a maintenance treatment. If so, DTMS treatment applied in constant intervals may prevent rather than treat relapses.

5. Conclusions

A second course of deep TMS in treating relapse of major depression is a feasible option that needs further investigation.

Competing interests

Prof. Dannon and Dr. Rosenberg received an unrestricted educational grant for TMS research from Brainsway Company.

Prof. Zangen serves as a research consultant and has financial interest in Brainsway Company.

Dr. Isserles receives financial support from Brainsway Company.

Prof. Levkovitz serves as consultant and has a financial interest in Brainsway Inc.

Authors' contributions

All authors read and approved the final manuscript.

Rosenberg Oded participated in the Deep transcranial magnetic stimulation treatments described in the text, in writing the basic draft of the paper and re-writing the text according to co-authors suggestions, in the discussion and conclusions, in the clinical evaluations, and has conducted statistics.

Isserles Moshe participated in the deep transcranial magnetic stimulation treatments, in writing discussion and conclusions, and in clinical evaluations.

Levkovitz Yechiel participated in the discussion and conclusions.

Kotler Moshe participated in the final approval of the manuscript.

Zangen Abraham participated by making extensive suggestions, advised on background, methods, discussion and conclusions, and navigated the paper scientifically.

Dannon Pinhas participated by contributing remarks and suggestions to the text, including discussion and conclusions, supervised closely the DTMS sessions as well as conducted part of the Deep transcranial magnetic stimulation treatments.

Role of funding sources

Rosenberg Oded — works in Beer Yaakov mental health Center and being paid by research fund of Beer Yaakov mental health Center.

Isserles Moshe — works in Hadassah Medical Center and gets paid by research fund of Hadassah Medical Center and also receives financial support from Brainsway Company.

Levkovitz Yechiel — works in Shalvata Mental Health Center as Senior psychiatrist and also serves as consultant of Brainsway.

Kotler Moshe — serves as the director of Beer Yaakov mental health Center.

Zangen Abraham — works in Department of Neurobiology of Weizmann Institute of Science and also serves as a research consultant and has financial interest in Brainsway Company.

Dannon Pinhas — serves as the head of research department of Beer Ya'acov mental health Center and head of ECT unit of Beer Yaakov mental health Center. Prof. Dannon is being paid by Beer Yaakov mental health Center.

Written consent for publication was obtained from the patients.

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