Long-term Follow-up of MDD Patients Who Respond to Deep rTMS: A Brief Report

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ABSTRACT

Background: Deep transcranial magnetic stimulation (dTMS) is effective in treatment of Major Depressive Disorder (MDD), and in re-treatment in case of relapse. Our study evaluates the long-term durability of dTMS in MDD.

Method: Seventeen patients that responded to dTMS treatment evaluated. Follow-up period was 9.3 months. Patients were considered as relapsed if: HDRS (Hamilton Depression Rating Scale) score was 16 points or more, in case of change in antidepressants, hospitalization due to exacerbation, referral to ECT.

Results: Six months after last treatment three patients relapsed (17.6%). During the follow-up of 9.3 months, nine relapsed. Relapse rate was 5.6 per 100 person-months. Patients continued to improve in HDRS following the treatment. We have found number of treatment sessions, stimulation, age, age of depressive disorder onset, length of depressive episode prior to the first treatment, as well as number of depressive episodes to have no predictive value regarding propensity to relapse in these patients.

Limitations: The study’s main limitations are the relatively small sample size, patients differing in follow-up periods and the lack of a control group.

Conclusion: Relapse rates after dTMS are comparable to pharmacotherapy and ECT.

INTRODUCTION

Depression is the leading cause of disability when measured by years living with the disability and is the fourth leading contributor to the global burden of disease in 2000, according to the World Health Organization. Despite pharmacological interventions, the long-term outcome of major depressive disorder (MDD) is poor, with psychiatric studies revealing high rates of relapse and extensive disability or suicide. Moreover, MDD is a recurring illness and residual symptomatology remains after the acute episode (1).

Treatment resistant depression (TRD) affects as many as 30% of patients with major depression; and in addition to lower treatment response, it is associated with higher suicide risks, relapse rates, and health care utilization costs (2). Treatment methods shown to be effective in the treatment of depression are pharmacotherapy, cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS) (1, 3-5).

Yiend et al. (5) reported that 73% of patients treated with pharmacotherapy underwent at least one recurrence of depression within 23 years. Other researchers reported a variation of 21% to 95% in relapse rates in 25 years (6-9).

Yiend et al. (5) also reported that the majority of the patients treated with pharmacotherapy had at least two or more episodes, and some had up to six episodes.

Wilkinson et al. (4) reported one-year recurrence rates of 27.8% and 44.4% in patients randomly allocated to a combination of CBT and antidepressant medications or an antidepressant alone, respectively. Bockting et al. (10) assessed relapse/recurrence of major depression over two years’ duration in patients randomized to treatment with continuation of pharmacotherapy, or to treatment aug-
ment with brief cognitive therapy. They found that cognitive therapy reduced relapse/recurrence from 72% to 46%.

ECT, which is considered one of the most effective treatments for depression (3), is widely used for the management of severe and refractory depression (11). However, ECT is associated with adverse cognitive effects and general anesthesia-associated risks, especially in patients with clinical co-morbidities. In addition, ECT induces seizures and causes significant memory and learning impairments (12). In major depression, the efficacy of ECT is well documented in the acute phase of the treatment (11). However, Wijkstra et al. (13) demonstrated that the 6-month relapse rate of depressed patients that have been treated with ECT was 50% (13).

Naturalistic studies show that the relapse rate during the 6 to 12 months following ECT exceeds 50% (14). Sackeim et al. (14) concluded that without active treatment virtually all remitted patients relapse within 6 months of stopping ECT (14), while the Consortium for Research in Electroconvulsive Therapy (CORE) reported relapse rates over 6 months to be 37.1%.

Repetitive TMS (rTMS) is considered a refined alternative for ECT in TRD (12). TMS is a non-invasive form of brain stimulation, which is thought to induce significant antidepressant effects with a few mild side effects and with no need for anesthesia (3).

Studies comparing the antidepressant effects of electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) have reached mixed results demonstrating that rTMS is inferior to ECT or effective as ECT in the treatment of major depression.

Eranti et al. randomly assigned 46 patients with major depression to either a 15-day course of rTMS of the left dorso-lateral prefrontal cortex or a standard course of ECT, and found that HAM-D scores at the end of the treatment were significantly lower for ECT, with 13 patients (59.1%) achieving remission in the ECT group and four (16.7%) in the rTMS group. However, at six months the HAM-D scores did not differ between groups. They concluded rTMS to be less effective than ECT, and ECT was substantially more effective for the short-term treatment of depression. TMS protocol included a total of 15,000 magnetic pulses for 15 days – a relatively low dose of magnetic stimulation making the comparison between the two stimulation methods questionable. Dannon et al. and Rosa et al. (1, 3) found the efficacy of ECT and rTMS to be similar in treating major depression. Dannon et al. (1) had reported that relapse rates in MDD patients treated with either rTMS or ECT are similar and close to 25% during the six months after treatment.

Grunhaus et al. (16) studied 40 patients with MDD randomly assigned to rTMS/ECT. Patients were treated using the following rTMS parameters: 90% power of the motor threshold, frequency of 10 Hz, 20 trains for 20 treatment days. Electroconvulsive therapy was performed according to standard protocols. Grunhaus and his colleagues found that patients with MDD and psychosis responded significantly better to ECT, whereas MDD patients without psychosis responded similarly to both treatments.

Pridmore et al. (17) compared the antidepressant effects of rTMS and ECT in 32 patients suffering major depressive episode. Treatment was continued until remission occurred or response plateaued. Pridmore and his colleagues found a significant main effect for treatment type reflecting an advantage for ECT patients on measures of depression overall.

Janicak et al. (18) studied 25 patients randomly assigned to rTMS (10-20 treatments, 10 Hz, 110% motor threshold applied to the left dorsolateral prefrontal cortex for a total of 10,000-20,000 stimulations) or a course of bitemporal ECT(4-12 treatment). Janicak and his colleagues found these two techniques to have comparable therapeutic effects.

O’Connor et al. (19) treated 14 patients with unilateral electroconvulsive therapy three times per week for 2 to 4 weeks and 14 with repetitive transcranial magnetic stimulation (1600 stimuli at 10 Hertz and 90% of motor threshold intensity to the left dorsolateral prefrontal cortex daily) for 2 consecutive weeks. O’Connor and his colleagues found electroconvulsive therapy to have a more positive effect on mood than rTMS but to exert a transient deleterious effect on various components of memory.

Schulze-Rauschenbach et al. (20) treated 30 patients with an average of ten treatments with either unilateral ECT or left prefrontal rTMS and assessed these patients for objective and subjective cognitive impairments before and about a week after treatment. Schulze-Rauschenbach and his colleagues found the two treatment methods to have comparable effects on treatment-remitted patients, but different cognitive outcomes: In patients treated with rTMS, cognitive performance remained constant or improved and memory complaints alleviated, whereas in the ECT group memory recall deficits emerged and memory complaints remained.

Previous research and clinical trials demonstrated that ECT seems more effective in general but cognitive impairment is a major drawback. Additional studies with larger samples are required in order to find out which of the treatments is preferable.

Janicak et al. (21) studied patients who randomly received active or sham rTMS. Ten of 99 patients relapsed. The
authors concluded that the therapeutic effects of rTMS are durable and that rTMS may be successfully used as an intermittent rescue strategy to preclude impending relapse (21).

Deep (D) TMS for indication of antidepressants resistant major depression was approved by the FDA in 2013. DTMS was previously shown to be effective in treating major depression (12, 22-25), though long-term follow-ups have not been reported yet. DTMS, as opposed to conventional rTMS, can stimulate fibers connecting the subgenual cingulate gyrus to the prefrontal cortex, thereby inducing an antidepressant action (23). DTMS efficacy in treating major depression is predictable considering the success of rTMS since in both methods the left dorso-lateral prefrontal cortex is being stimulated.

METHODS
This study was approved by the Institutional Review Board (IRB) and conducted at Beer Yaakov Mental Health Center. Enrollment of patients took place from January 2008 through August 2009; all patients were recruited as referrals from psychiatrists from Beer Yaakov-Ness Ziona Mental Health Complex. All patients gave informed consent to participate in this study. Previously, we treated 31 patients suffering from MDD with dTMS. The treatment results of these 31 patients have been published (22-25).

Prior to dTMS treatment, patients were diagnosed with major depression according to DSM-IV-TR criteria, except one, who was diagnosed with Bipolar II Disorder. Patients failed to respond to at least two antidepressant trials with adequate dosage and duration of treatment.

Within the group of 31 patients that we studied, 17 patients (Table 1) responded to treatment (we considered treatment response to be an HDRS-24 improvement of >50%, and remission to be a score <10 [27]. Eight of the 17 patients were treated with antidepressant medications before and during Deep TMS treatment and at the follow-up period. No switching, augmentation, addition or dosage escalation took place during dTMS treatment or during the follow-up period. Three patients underwent ECT at least six months prior to dTMS treatment, while three others also underwent dTMS at least six months prior to dTMS treatment (Table 2).

The participants’ ages ranged from 24 to 63 years (46 ± 12.1). Average age of depressive disorder onset was 31.5 ± 14 years. Average length of depressive episodes prior to the first treatment was 10.7 ± 10.2 months. Kellner et al. (26) defined relapse as a patient’s HDRS-24 total score of

| Age | Sex | Age of depressive disorder onset | Length of depressive episode prior to the first treatment (months) | Number of depressive episodes | Antidepressants during treatment | Number of daily treatments | Number of maintenance treatments | Relapse | Follow-up time points: Time elapsed between last treatment and relapse/evaluation (months) |
|-----|-----|----------------------------------|---------------------------------------------------------------|-------------------------------|----------------------------------|---------------------------|--------------------------------|--------|---------------------------------------------------------------------------------
| 37  | female | 22 | 20 | many | No | 20 | 1 | no relapse | 6 |
| 58  | male | 12 | 6 | many | No | 20 | 4 | no relapse | 11.67 |
| 36  | female | 27 | 12 | many | Trazodone | 15 | 0 | relapse (hospitalized) | 13.8 |
| 63  | female | 47 | 1 | 4 | Citalopram, Lamotrigine | 20 | 0 | relapse (hospitalized) | 1 |
| 35  | male | 25 | 6 | 6 | Mianserin | 20 | 4 | relapse | 7.7 |
| 40  | male | 25 | 0.5 | many | Paroxetine | 20 | 3 | relapse | 11.8 |
| 24  | male | 20 | 18 | 3 | No | 19 | 0 | relapse | 10.3 |
| 28  | female | 26 | 30 | many | Trazodone | 20 | 4 | no relapse | 7.3 |
| 56  | male | 27 | 12 | many | Escitalopram | 17 | 0 | no relapse | 14.5 |
| 55  | female | 54 | 10 | 3 | No | 20 | 0 | no relapse | 27.4 |
| 55  | male | 48 | 24 | 2 | No | 20 | 4 | no relapse | 6.8 |
| 53  | male | 10 | 7 | 4 | No | 19 | 0 | relapse | 6 |
| 59  | male | 58 | 1 | 3 | No | 20 | 3 | no relapse | 6 |
| 55  | female | 38 | 2 | many | Escitalopram | 20 | 3 | no relapse | 6 |
| 48  | female | 25 | 1 | many | No | 20 | 1 | relapse | 10.8 |
| 32  | male | 29 | 30 | 1 | Escitalopram | 19 | 0 | relapse | 15 |
| 47  | male | 43 | 2 | many | No | 20 | 4 | relapse | 9.5 |
16 or higher in two consecutive ratings. Dannon et al. (1) defined relapse as a return of depressive symptomatology meeting DSM-IV criteria for MDD with an HDRS of 16 or more points. We have chosen to define relapse as an HDRS rating of 16 or more. In this article we report the results of one month to 27 months follow-up of depressive patients treated with dTMS. This is the first study evaluating the long-term outcome of dTMS in the treatment of depression.

DEEP TMS
DTMS treatment was performed with Brainsway’s H1 coil connected to a Magstim Rapid2 stimulator. High-frequency TMS sessions consisted of 42 trains of 20 Hz for two seconds, with inter-train interval (ITI) of 20 seconds (1,680 pulses in total). Treatment included 20 rTMS sessions on consecutive days and additional four weekly sessions. Technical information regarding the dTMS method and treatment procedure is detailed in a previous study (26).

EVALUATION OF LONG-TERM EFFICACY
Seventeen patients who responded to the dTMS treatment were followed up for up to 27 months after treatment. Patients were evaluated using the same evaluation scales as those used for the evaluation at the active treatment sessions: the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), and the Beck Depression Inventory (BDI).

Patient relapse was defined as follows: 1) HDRS score was 16 or more points at the follow-up period; 2) hospitalization due to depression exacerbation; and 3) any change in antidepressant medications including switching, augmentation, addition, and dosage escalation following a psychiatric evaluation; and 4) referral to ECT or any other neuro-stimulation treatment.

STATISTICAL ANALYSIS
Results are presented as means +/- SD. Significance of differences in HDRS-24, HARS, and BDI scores between relapsed and non-relapsed patients was determined by repeated-measures ANOVA, followed by Fisher’s least significant difference post-hoc test. The effect of the number of treatment sessions, stimulation intensity, medication, and demographics on relapse was assessed by an unpaired two-tailed t-test. All analyses were done with Statistica 8.0. A p-value of less than 0.05 was considered statistically significant.

RESULTS
All patients were followed during six months after treatment; some patients continued follow-up for up to 27 months. Mean follow-up period was 9.3 months At six months of follow-up time point treatment, only three out of 17 patients had relapsed (17.6%).

During the extended follow-up, 9.3 months on average, nine patients relapsed and eight patients did non-relapse. The relapse rate was 5.6 per 100 person-months.

NON-RELAPSED PATIENTS
Eight patients (four males, four females, mean age 50.37+11.39) did not relapse during the follow-up period. Moreover, they continued to improve after the last treatment session (not statistically significant, P value>0.05). Those patients completed the DTMS treatment with HDRS average score of 9.37+4.17, average HARS of 8.1+4.9, and average BDI of 10.8+6.7. At the follow-up visit the HDRS score was 5.5+3.11, HARS score was 6+3.3, and BDI average score was 8.6+4.2. Of these eight patients, three (37.5%) were treated with antidepressants.

RELAPSED PATIENTS
Nine patients (six males, three females, mean age 42+11.9) relapsed. One patient was admitted for hospitalization due to depressive exacerbation one month after the last dTMS session. A second patient was admitted for hospitalization due to depressive exacerbation accompanied by suicidal ideation 13 months after the last dTMS session. A third patient was followed-up in an ambulatory clinic of Beer Yaakov and needed antidepressant replacement due to depressive exacerbation six months after the last dTMS session. The remaining six patients relapsed according to the HDRS score. Even though the end of treatment
effect was not kept, they had a better HDRS score at the follow-up compared to their pre-treatment HDRS.

Those remaining six patients had an average HDRS score of 27.17 +3.19 before treatment, completed the dTMS treatment with an HDRS average score of 5.7 +5.8, an average HARS of 6.3 +5.57, and an average BDI of 10.3+8. At the follow-up visit the HDRS score was 21.5 +4.3, HARS score was 18.3 +7, and BDI average score of 25.5 +6.8. Paired t-test for the HDRS score at the follow-up compared to HDRS score before treatment revealed a significant lower HDRS score with P value 0.019.

Of the nine patients that relapsed, five (55.5%) were treated with antidepressants.

COMPARISON OF THE TWO GROUPS

**HDRS-24**

Repeated-measures ANOVA with group (relapsed versus non-relapsed) as between-subjects factor and time points (before treatment, immediately after treatment, and at follow-up) as within-subjects factor revealed a significant main effect of group (F[1,15]=10.6, p=0.005), time (F[2, 15]=124, p<0.001), and interaction (F[2,15]=35.5, p<0.001) (Figure 1A). Post-hoc analysis showed that HDRS-24 in relapsed patients differed from patients that did not relapse only at the follow-up (p<0.001), but not before and after dTMS treatment.

**BDI**

Repeated-measures ANOVA with group as between-subjects factor and time points as within-subjects factor revealed a significant main effect of group (F[1,15]=4.96, p=0.042), time (F[2, 15]=63.15, p<0.001), and interaction (F[2,15]=26.97, p<0.001) (Figure 1B). Post-hoc analysis showed that BDI in relapsed patients differed from patients that did not relapse only at the follow-up (p<0.001), but not before and after dTMS treatment. HARS

Repeated-measures ANOVA with group as between-subjects factor and time points as within-subjects factor revealed a significant main effect of time (F[2, 15]=45.08, p<0.001) and interaction (F[2,15]=18.63, p<0.001), but not of group (Figure 1C). Post-hoc analysis showed that HARS in relapsed patients was lower than in those that did not relapse before treatment (p=0.044) and became higher at the follow-up (p<0.001).

COMPARISON OF OTHER PARAMETERS

Differences between the two groups were measured in all optional predictive values (see Table 1).

DISCUSSION

We followed 17 patients who were treated with Deep TMS for major depression and responded. The relapse rate in our study is comparable to other studies (21). We have found that the HDRS average score
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Long-term Follow-up of MDD Patients Who Respond to Deep rTMS


Long-term follow-up of MDD patients who responded to deep TMS treatment was lower than their pre-treatment average score. This result supports our theory in what regards the durability of dTMS effect. HDRS and BDI scores of patients who retained a non-relapsed state improved compared to their last evaluation at the end of treatment. Although the aforementioned improvement was not statistically significant and may be due to the small sample size, the fact that these patients did not relapse supports the assumption that dTMS effect is durable.

Triggs et al. (28) conducted a prospective, randomized, sham-controlled, double blind, parallel group study of right or left pre-frontal rTMS in 48 subjects with medication-resistant depression. In both real and sham groups rTMS Hamilton depression scores continued to improve even three months following completion of rTMS (28). Hamilton depression scores’ long-term improvement following sham rTMS makes it difficult to decide whether TMS long-term anti-depressive effect is related to brain changes.

Cohen et al. (29) identified the number of sessions as an independent predictor of long-term benefits. In our study, the number of sessions had no predictive value.

We also found that HDRS or BDI scores at the end of treatment did not have a predictive value regarding efficacy persistence.

Janicak et al. (21) reported on 99 major depressive patients treated with rTMS to the left dorsolateral prefrontal cortex. Of these, 77.8% had achieved full response or greater benefit (i.e., at least 50% or greater reduction of HAMD-17 total score from baseline), while 22.2% achieved partial response. Patients were tapered off rTMS over three weeks, simultaneously starting maintenance antidepressant mono-therapy. Relapse was the primary outcome measure, and was defined as a recurrence of full DSM-IV criteria for major depression for two consecutive weeks. Patients were then followed for 24 weeks in a naturalistic follow-up study examining the long-term durability of rTMS. Ten of 99 patients (10%) relapsed while 38 patients (38.4%) met the criteria for symptom worsening. Patients with a more robust acute response to active rTMS were less likely to relapse or require rTMS reintroduction than those with a partial response. This fact contrasts with our results since we discovered no statistical differences in HDRS scores after dTMS treatment between relapsed and non-relapsed groups.

Data on gender differences in depression relapse/recurrence are conflicting: Data on 2,541 participants enrolled in the STAR*D study show that men reported additional previous episodes (=higher rates of relapse) of major depression (30). In contrast, higher rates of relapse and recurrence for females have been reported (31, 32). In a co-morbidity survey, rates of relapse and chronicity were not associated with gender (33). In our study, six of ten (60%) males relapsed while three of seven (43%) women relapsed. Although our results are limited by the small sample size, they are in accordance with the STAR*D study.

The mean age of relapsed patients was 42 while the mean age of patients staying in remission was 50. Cohen et al. (29) identified younger age as an independent predictor of long-term benefits. The difference that was shown in our study was not statistically significant and probably was caused by chance.

Five of eight patients treated with medications relapsed (62%). Among the nine drug-free patients, four patients relapsed (44%). HDRS results at follow-up between antidepressant treated and non-treated patients showed that medication has no add-on effect on outcome.

Schüle et al. (34) examined whether antidepressant pharmacotherapy can stabilize clinical improvement after rTMS mono-therapy in 26 drug-free patients suf-
ferring from a major depressive episode. They concluded that antidepressant pharmacotherapy is able to further improve the clinical response to rTMS and that responders to rTMS mono-therapy should receive subsequent psychopharmacological treatment without interruption in order to avoid a deterioration of symptoms. In our study there was no statistical difference between patients treated with dTMS as an add-on therapy to medications or treated by dTMS alone. In our study patients treated with medications were under medication prior to enrollment as well as during enrollment, while in the aforementioned study, medications started after rTMS treatment.

Fitzgerald et al. (35) reported 19 re-treated patients (16 diagnosed with major depression and three with Bipolar Disorder), who were previously treated with TMS. Patients were allocated either for left High Frequency rTMS, right Low Frequency rTMS, or a combination of both treatment modalities. The mean duration of time between first rTMS treatment and re-treatment was 10.5 ±6.6 months. Seventeen of 19 patients were on antidepressant medication during re-treatment. In our study mean time to relapse was 8.4.8 months ranging from one month to 13.8 months. Time to relapse is similar between both studies, although in the Fitzgerald et al. (35) study treatment was given using a figure of eight coil in different locations and frequencies while we applied 20 HZ stimulation frequency using a deep TMS H1-coil. Dannon et al. (1) reported mean time to relapse of 6.9 ±4.8 months in four patients previously treated successfully with 10HZ (figure of eight coil) to the dorsolateral prefrontal cortex. Two of these patients were on antidepressant medication (1).

In our study, nine patients relapsed, with mean time to relapse being 8 ±4.8 months ranging from one month to 13.8 months. Demirtas-Tatlidede et al. (36) reported 16 patients who were treated repeatedly (a mean of four treatment courses) with ten sessions of 10 HZ rTMS to the left dorsolateral prefrontal cortex. Patients were treated repeatedly with rTMS when HAM-D score was equal approximately to previous pretreatment scores (often well beyond 18 points). Mean interval between treatments was 4.9 ±3.8 months. Fifty percent of patients in this study were medication-free (36). Although time length to relapse cannot be compared between this study and our own because of multiple courses given in the first, a durability effect of rTMS may be concluded.

Data from 172 remitted recurrently depressed patients over a 5.5-year follow-up period disclosed a number of previous episodes to be predictive of future depressive episodes (37). Four of the nine (44%) relapsed patients and five of the eight (62%) staying in a non-relapsed state had many (10+) depressive episodes. This apparent discrepancy may be explained by the small sample size of our study.

Depression is unlikely to be a disease of a single brain region or neurotransmitter system, but rather a system level disorder, affecting integrated pathways. One system in particular receiving much attention in the study of depression is the reward circuit, whose main component is the mesolimbic dopaminergic pathway. Treating depression with direct stimulation of deeper regions might be more effective than the superficial TMS treatment. In dTMS treatment effects, deeper layers of the prefrontal cortex are interconnected with reward-related brain sites such as the ventral striatum and the ventral tegmental area.

The study’s limitation is the relatively small sample size, patients differ in follow-up periods, the uncertainty regarding unreported depressive episodes in-between treatment termination and long-term evaluation, lack of control group (treatment as usual group), non-blinded naturalistic design, mix of medicated and not medicated subjects, lack of direct comparative studies and the variance in number of treatment sessions.

CONCLUSION

DTMS relapse rates are at least comparable to other methods of major depression treatment. Moreover, treatment effect is durable and maintained even in relapsed patients in the sense that their level of depression is lower than prior to treatment. Medication treatment does not have an add-on effect to dTMS treatments in regard to relapse prevention. No measure or demographic data may be used to predict the propensity of dTMS treatment successes in a depressed patient. Further studies are required in order to establish dTMS as first line treatment for treatment resistant depression, either as an adjunct to pharmacotherapy or as a sole treatment.

References


