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

Oded Rosenberg, MD,[1] Limor Dinur Klein, MSc,[1] Roman Gersner,PhD,[2] Moshe Kotler, MD,[1] Abraham Zangen, PhD,[3] and Pinhas Dannon,MD[1]

[1] *Beer Ya'acov Mental Health Center affiliated to Sackler School of Medicine, University of Tel Aviv, Tel Aviv, Israel*
[2] *Department of Neurology, Children's Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.*
[3] *Faculty of Natural Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

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-

Address for Correspondence: ✉ Oded Rosenberg, MD, Beer Ya'acov Mental Health Center, POB 1, Beer Ya'acov 70350, Israel
odedaruna@gmail.com

mented 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 efficacy 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 anti-depressants 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

Table 1. *Demographic Data*

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	1.5
47	male	43	2	many	No	20	4	relapse	9.5

Table 2. *Brain Stimulation History of Six Patients*

Patient No.1	Patient underwent ECT 3 years prior to present depressive episode with mild improvement and severe amnesia	Relapsed
Patient No.2	Patient underwent 2 ECT courses the last being one year before enrollment. Patient did not improve after the last ECT.	No relapse
Patient No.3	Patient underwent 2 ECT courses which were partially successful	No relapse
Patient No.4	Patient underwent one deep TMS course six months before enrollment, with partial response (HDRS dropped from 30 to 21)	No relapse
Patient No.5	Patient underwent one deep TMS course one year before enrollment with remission (HDRS dropped from 27 to 1)	No relapse
Patient No.6	Patient underwent one deep TMS course one year before enrollment with response (HDRS dropped from 24 to 12)	No relapse

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

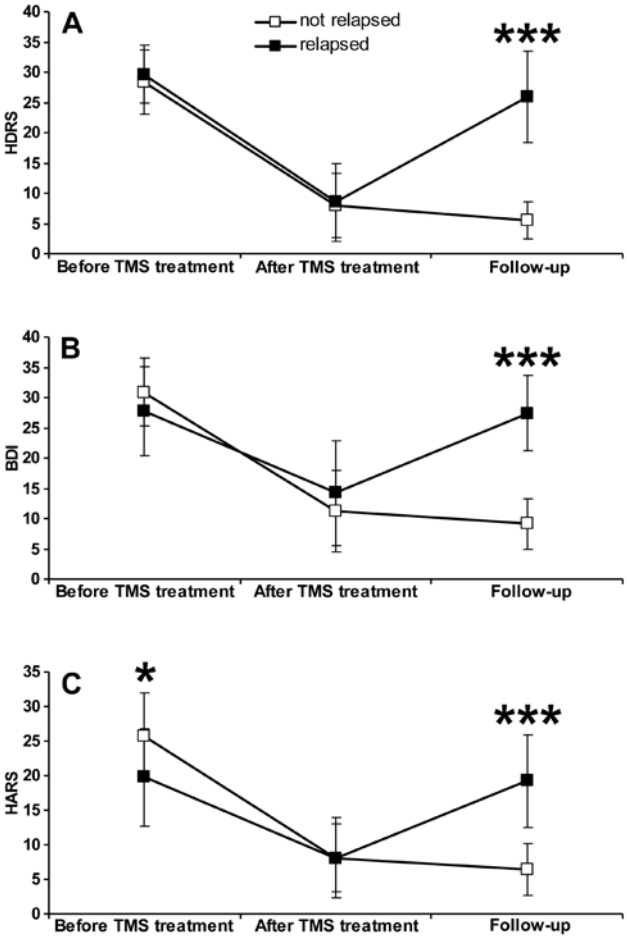
Repeated-measures ANOVA with group as between-subjects factor and time points as within-subjects factor revealed a significant main effect of group ($F[1,15]=4.96$, $p=0.042$), time ($F[2, 15]=63.15$, $p<0.001$), and interaction ($F[2,15]=26.97$, $p<0.001$) (Figure 1B). Post-hoc analysis showed that 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).

Figure 1. *Effects of deep rTMS treatment and relapse on HDRS (A), BDI (B) and HARS (C) before treatment, after treatment and at follow-up. Data are presented as mean ± SD*



* $p<0.05$, *** $p<0.001$ as compared between relapsed and not relapsed patients at specific time points.

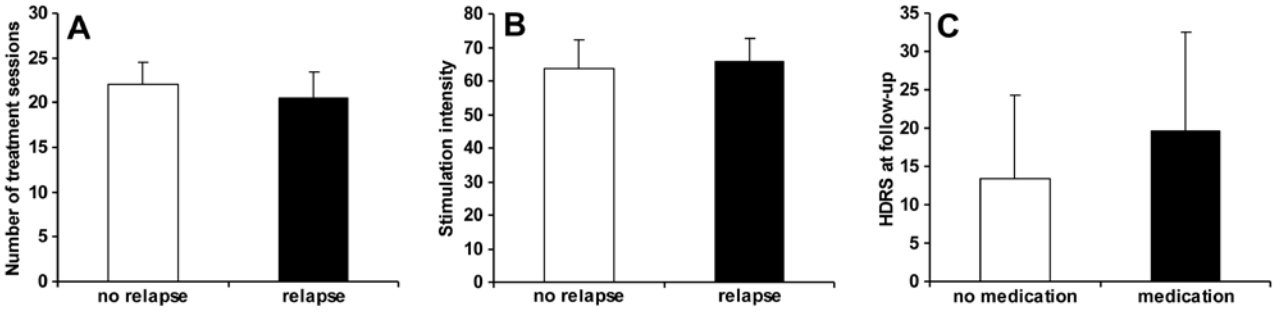
The number of treatment sessions ($t:[15]=1.17$, NS, Figure 2A) and stimulation intensity ($t:[15]=0.5$, NS, Figure 2B) were not different between relapsed and non-relapsed patients. Other parameters such as age, age of depressive disorder onset, length of depressive episode prior to the first treatment (months), and number of depressive episodes were also not significantly different between relapsed and non-relapsed patients.

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

Figure 2. *Effects of number of treatment sessions (A), stimulation intensity (B) and medication (C) on relapse. Data are presented as mean ± SD. No significant differences between the groups*



of relapsed patients six months (and even more) after dTMS 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-

fering 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

1. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three- and six-month outcomes following courses of either ECT or rTMS in a population of severely depressed individuals - preliminary report. Biol Psychiatry 2002;51:687-690.
2. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry 2006;67:688-695.
3. Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: A randomized, single-blind study. Int J Neuropsychopharmacol 2006;9:667-676.

4. Wilkinson P, Alder N, Juszczak E, Matthews H, Merritt C, Montgomery H, et al. A pilot randomized controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. Int J Geriatr Psychiatry 2009;24:68-75.
5. Yiend J, Paykel E, Merritt R, Lester K, Doll H, Burns T. Term outcome of primary care depression. J Affect Disord 2009;118:79-86.
6. Angst J, Preisig M. Course of a clinical cohort of unipolar bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995;146:5-16.
7. Kennedy N, Abbott R, Paykel ES. Remission and recurrence of depression in the maintenance era: Long-term outcome in a Cambridge cohort. Psychol Med 2003;33:827-838.
8. Kiloh LG, Andrews G, Neilson M. The long-term outcome of depressive illness. Br J Psychiatry 1988;153:752-757.
9. Lee AS, Murray RM. The long-term outcome of Maudsley depressives. Br J Psychiatry 1988;153:741-751.
10. Bockting CL, Schene AH, Spinhoven P, Koeter MW, Wouters LF, Huyser J, Kamphuis JH. Preventing relapse/recurrence in recurrent depression with cognitive therapy: A randomized controlled trial. J Consult Clin Psychol 2005;73:647-657.
11. Medda P, Perugi G, Zanello S, Ciuffa M, Cassano GB. Response to ECT in bipolar I, bipolar II and unipolar depression. J Affect Disord 2009;118:55-59.
12. Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, et al. Deep transcarnial magnetic stimulation over the prefrontal cortex: Evaluation of antidepressants and cognitive effects in depressive patients. Brain Stimul 2009;2:188-200.
13. Wijkstra J, Nolen WA, Algra A, van Vliet IM, Kahn RS. Relapse prevention in major depressive disorder after successful ECT: A literature review and a naturalistic case series. Acta Psychiatr Scand 2000;102:454-460.
14. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized controlled trial. JAMA 2001;285:1299-1307.
15. Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry 2007;164:73-81.
16. Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: An open study. Biol Psychiatry 2000;47:314-324.
17. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. Int J Neuropsychopharmacol 2000;3:129-134.
18. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: Preliminary results of a randomized trial. Biol Psychiatry 2002;51:659-667.
19. O'Connor M, Brenninkmeyer C, Morgan A, Bloomingdale K, Thall M, Vasile R, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: A neurocognitive risk-benefit analysis. Cogn Behav Neurol 2003;16:118-127.
20. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M, et al. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. Br J Psychiatry 2005;186:410-416.
21. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 2010; 3:187-199.
22. Isserles M, Rosenberg O, Dannon P, Levkovitz Y, Kotler M, Deutsch F, et al. Cognitive-emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome. J Affect Disord 2011;128:235-242.
23. Rosenberg O, Shoenfeld N, Zangen A, Kotler M, Dannon PN. Deep TMS in a resistant major depressive disorder: A brief report. Depress Anxiety 2010; 27:465-469.
24. Rosenberg O, Zangen A, Stryjer R, Kotler M, Dannon PN. Response to deep TMS in depressive patients with previous electroconvulsive treatment. Brain Stimul 2010;3:211-217
25. Rosenberg O, Isserles M, Levkovitz Y, Kotler M, Zangen A, Dannon PN, et al. Effectiveness of a second deep TMS in depression: A brief report. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1041-1044.
26. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: A multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006;63:1337-1344.
27. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: Remission, recovery, relapse and recurrence. Arch Gen Psychiatry 1991;48:851-865.
28. Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: A randomized, sham-controlled trial. Psychiatry Res 2010; 178:467-474.
29. Cohen RB, Boggio PS, Fregni F. Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. Depress Anxiety 2009;26:682-688
30. Marcus SM, Kerber KB, Rush AJ, Wisniewski SR, Nierenberg A, Balasubramani GK, et al. Gender differences in depression symptoms in treatment-seeking adults: STAR*D Confirmatory Analyses. Compr Psychiatry 2008;49:238-246.
31. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999;156:1000-1006.
32. Bracke P. Sex differences in the course of depression: Evidence from a longitudinal study of a representative sample of the Belgian population. Soc Psychiatry Psychiatr Epidemiol 1998;33:420-429.
33. Kessler RC, McGonagle KA, Swartz M ,Blazer DG,Nelson CB. Sex and depression in the national comorbidity survey I: Lifetime prevalence, chronicity and recurrence. J Affec Dis 1993;29:85-96.
34. Schüle C, Zwanzger P, Baghai T, Mikhaiel P, Thoma H, Möller HJ, et al. Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: An open follow-up study. J Psychiatr Res 2003;37:145-153.
35. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J. Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. Aust N Z J Psychiatry 2006;40:764-768.
36. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, Pearlman C, Stern WM, Thall M, et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: Reproducibility and duration of the antidepressant effect in medication-free patients. J Clin Psychiatry 2008;69:930-934.
37. Doesschate MC, Bockting CL, Koeter MW, Schene AH. Prediction of recurrence in recurrent depression: A 5.5-year prospective study. J Clin Psychiatry 2010;71:984-991.