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Augmenting antidepressants with deep transcranial magnetic stimulation (DTMS) in treatment-resistant major depression

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ABSTRACT

Background: Deep transcranial magnetic stimulation (DTMS) has been shown to be efficacious and relatively safe for major depressive disorder (MDD). However, its clinical utility as an augmenting strategy for treatment-resistant depression (TRD) remains unexplored.

Methods: In an open label trial, 17 outpatients with severe TRD received 4 weeks of daily high frequency DTMS over the left dorsolateral prefrontal cortex. Depressive and anxious symptoms, suicidality and quality of life (QOL) were measured at baseline (i.e., in the week prior to the start of the DTMS treatment) and at week 5 (i.e., in the week following the end of the DTMS treatment). Primary outcome measures were rates of response and remission at week 5 using an intention-to-treat approach.

Results: Response and remission rates at week 5 were 70.6% and 41.2%, respectively. Also, depression, anxiety, and suicidality ratings were significantly improved by week 5 (with Hedges' *g* estimates ranging from 0.6 to 1.72), as well as 4 of the 5 QOL domain scores (i.e., global, psychological, environmental and social). Finally, two patients dropped out of the study at week 1 because of significant scalp discomfort during stimulation.

Conclusions: Our study suggests that DTMS, when used as an augmenting strategy for antidepressants in severe TRD, is efficacious, safe and relatively well tolerated. However, controlled studies with larger samples are needed to confirm and expand our preliminary findings.

Keywords: Unipolar major depression; Transcranial magnetic stimulation; Prospective study; Treatment-resistant depression; Quality of life.

Although pharmacological interventions remain the cornerstone of the medical management of major depressive disorder (MDD), they are often unable to yield adequate clinical improvement in a relatively large portion of patients (Kupfer et al. 2012). In fact, up to 20-30% of subjects suffering from MDD remain significantly ill despite the use of multiple therapeutic approaches (Berlim et al. 2008) and, as demonstrated by the large STAR*D study, less than a third of them will achieve remission within 12 weeks of starting a first-line antidepressant (Trivedi et al. 2006). These patients usually present with treatment-resistant depression (TRD) (Berlim and Turecki. 2006;Dunner et al. 2006), and growing evidence suggests that this condition is associated with high levels of morbidity, chronicity and societal costs (Greden. 2001;Dunner et al. 2006). Therefore, appropriate clinical management of TRD is of paramount clinical importance (Fava. 2003;Vieta and Colom. 2011).

A promising therapeutic intervention for managing TRD is high frequency repetitive transcranial magnetic stimulation (HF-rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) (Gershon et al. 2003;Padberg and Moller. 2003;Loo and Mitchell. 2005;Mitchell and Loo. 2006;Berlim et al. 2008). This non-invasive procedure involves the safe induction of electrical currents within the brain produced by pulsating magnetic fields generated through a coil-of-wire near the scalp (Daskalakis et al. 2008). These currents, in turn, can modulate cortical excitability in relatively focused brain regions (Fregni and Pascual-Leone. 2007;Wassermann and Zimmermann. 2012). Several meta-analyses have shown that HF-rTMS is associated with clear antidepressant properties (Lam et al. 2008;Slotema et al. 2010;Allan et al. 2012;Berlim et al. 2014), and the largest randomized controlled trial (RCT) in MDD published to date (n=301) has reported that active HF-rTMS is superior to sham HF-rTMS with associated response and remission rates of 27.7% and 20.6%, respectively (O'reardon et al. 2007). Interestingly, this RCT has also shown that a higher number of prior treatment failures, a longer duration of the current depressive illness, and the presence of a comorbid anxiety disorder predicted a worse clinical response to HF-rTMS treatment

for MDD (Lisanby et al. 2009)).

More recently, a novel rTMS coil has been developed to enable the direct modulation of relatively larger and deeper brain regions (Roth et al. 2002;Zangen et al. 2005). This new "H1" coil (whose derived therapeutic application has been called deep transcranial magnetic stimulation [DTMS]) is able to maximize the electrical field deeper in the brain by summating separate fields projected into the skull from several points around its periphery, while minimizing the accumulation of electrical charges on the surface of the brain (Roth et al. 2002). A number of electric field distribution studies in human head models have shown that the H1 coil is associated with significantly higher stimulation depth and electrical field diffusiveness when compared to the conventional HF-rTMS figure-of-8 coil (Roth et al. 2007;Deng et al. 2013;Roth et al. 2014). These putatively broader neural effects of the H1 coil have led to the hypothesis, still not properly tested, that it might be associated with more robust clinical improvements (Levkovitz et al. 2007;Levkovitz et al. 2010;Bersani et al. 2013). The antidepressant effects of DTMS used as a monotherapy for MDD were initially demonstrated in a randomized feasibility trial involving 65 medication-free patients. Briefly, this study has shown that 4 weeks of daily treatment with the H1 coil (i.e., 20 sessions in total) was associated with response and remission rates of 47% and 42%, respectively (Levkovitz et al. 2010).

The clinical utility of DTMS as an augmenting strategy for antidepressants in TRD has been only partly explored, particularly in routine clinical care (Rosenberg et al. 2010;Rosenberg et al. 2010;Isserles et al. 2011). For example, Isserles and colleagues (Isserles et al. 2011) have recently reported a randomized trial including 46 patients with mild to moderate TRD and no Axis I comorbidity who were on stable medication regimens for at least 4 weeks before study entry and who received 20 daily sessions of DTMS combined with positive, negative or neutral cognitive-emotional reactivation procedures. Overall, response and remission rates at week 4 were 46% (n=21) and 28% (n=13), respectively. However, the augmentation of ineffective or partially

effective antidepressants with DTMS in severe TRD has not yet been investigated. To address this issue, we conducted a 4-week open label trial of daily DTMS over the left DLPFC in depressed patients who had not responded to at least 3 antidepressant trials in the current depressive episode. Compared to previous studies, we have employed a stimulation protocol involving significantly more magnetic pulses per session and this was based on preliminary findings from the HF-rTMS literature suggesting that more intensive treatments might result in faster and/or more pronounced antidepressant effects (Gershon et al. 2003;Holtzheimer et al. 2010;Baeken et al. 2014). We examined a relatively broad range of outcome variables, including symptom measures (e.g., subjective and objective depressive and anxious symptoms, suicidality), and subjective quality of life (QOL). We hypothesized that this more intensive DTMS protocol would be efficacious and well tolerated when used to treat patients with TRD from a "real world" clinical practice setting.

Participants and Methods

Depressed Patients

The present study was registered at www.clinicaltrials.gov (identifier # NCT01409304) and was approved by the Douglas Mental Health University Institute's (DMHUI) Research Ethics Board. Written informed consent was obtained from all participants. A total convenience sample of 17 depressed subjects (4 males, 13 females) were recruited between October 2011 and November 2012 from the Depressive Disorders Program at the DMHUI - a tertiary care outpatient clinic providing specialized follow up for individuals with moderate to severe MDD. All participants had a primary diagnosis, according to the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998), of a unipolar major depressive episode (MDE) of at least moderate intensity (i.e., a baseline score $\geq$ 18 on the 21-item Hamilton Depression Rating Scale [HAM-D_{21}] (Hamilton. 2000)). Also, they had to have failed to respond to at least three adequate courses of antidepressants (in terms of dose, duration and compliance) in the current MDE (as assessed by the

Antidepressant Treatment History Form (Sackeim. 2001)). Enrolled patients received no compensation for their participation in this study.

Patients were not withdrawn from psychotropics, but their doses were required to remain stable in the 4 weeks preceding this trial and for its entire duration. The only exceptions were benzodiazepine or non-benzodiazepine (e.g., zopiclone) hypnotics that could be used for the management of treatment-emergent insomnia in doses of up to 3mg/d of lorazepam (or equivalent).

Exclusion criteria included the presence of current psychotic features, lifetime history of any non-mood psychotic disorder, lifetime history of bipolar disorder types I or II, current substance or alcohol abuse/dependence (within the past six months), lifetime neurological disease (e.g., Parkinson's, stroke), pregnancy and/or presence of any contraindication for DTMS (e.g., personal history of epilepsy, metallic head implants).

Evaluation and Outcome Measurements

A psychiatrist (M.T.B.) performed baseline medical and psychiatric history assessments and safety screenings. Effectiveness data were gathered at baseline and at week 5 by the same psychiatrist (E.C.) who was not involved in the delivery of the DTMS treatment or in the daily clinical care of the enrolled participants.

Measures of depressive symptoms included the HAM-D_{21} (Hamilton. 1960) and the Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR_{16}) (Trivedi et al. 2004), whereas assessment of anxiety included the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton. 1959) and the Beck Anxiety Inventory (BAI) (Beck et al. 1988). The Clinical Global Impression - Severity (CGI-S) Subscale (Guy. 1976) was used to assess overall symptom severity and the Scale for Suicidal Ideation (SSI) (Beck et al. 1979) to evaluate suicidality. The Maudsley Staging Method (MSM) (Fekadu et al. 2009) was used to determine the level of patients' treatment-resistance whereas the Frequency/Intensity/Burden of Side Effects Rating Scale (FIBSER) (Wisniewski et al.

2006) was used to assess the presence and the intensity of treatment-emergent side effects. Finally, subjective QOL was evaluated with the 26-item World Health Organization's Quality of Life Measure – Brief Version (WHOQOL BREF) which measures five broad domains, namely physical, psychological, environmental, social and global) (Skevington et al. 2004).

Primary outcome measures were rates of response (i.e., ≥ 50% reduction in HAM-D_{21} scores) and remission (i.e., final HAM-D_{21} score ≤ 9) at week 5. Secondary outcome measures included pre-post DTMS changes in depression and anxiety scores as well as in QOL domains.

DTMS Treatment

DTMS was administered using a Magstim Rapid^2® magnetic stimulator (Magstim Company Ltd., U.K.) connected to an H1 coil (manufactured by Brainsway Inc., Israel) which produces its most effective electric field in the anterior-posterior axis with a preference for the left brain hemisphere (Roth et al. 2007)). Prior to stimulation, subjects were instructed to insert earplugs. The resting motor threshold (rMT) was determined on a weekly basis over the left primary motor cortex using the visualization method (Pridmore et al. 1998) and the maximum likelihood strategy (Mishory et al. 2004) (using the same H1 coil employed to deliver the DTMS treatments). The positioning of the H1 coil over the left DLPFC was performed by moving it 6 cm anteriorly to the rMT "hot-spot" (i.e., the point in the scalp in which a minimum magnetic field produced the largest motor twitch of the contralateral hand) parallel to the sagittal suture of the skull (Isserles et al. 2011;Levkovitz et al. 2011). To ensure placement reproducibility, spatial coordinates were marked on a cap placed on the subject's head. Each DTMS session consisted of 75 trains (2 seconds duration, 20-second inter-train interval) delivered at a frequency of 20 Hz (i.e., 3,000 pulses per session) and at an intensity of 120% of the rMT. In order to minimize significant scalp discomfort and thus enhance initial tolerability, the intensity of the DTMS treatment could be decreased to 100% of the rMT during the first week and then be gradually increased to 120% of the

rMT during the second week. Overall, patients received 4 weeks of daily DTMS, totaling 20 sessions and 60,000 magnetic pulses.

Statistical Analyses

Data were analyzed using Statistical Product and Service Solutions (SPSS) v. 20 (IBM Corporation, Chicago, IL, USA) within an intention-to-treat framework. Pre-post DTMS comparisons were performed with two-tailed paired *t*-tests. Hedges' *g* effect sizes for the continuous outcome measures were calculated using Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ, USA). We considered *g* values ≤ 0.39, 0.4 to 0.74, and ≥ 0.75 as indicating small, medium and large effect sizes, respectively (Grissom and Kim. 2012). Finally, $p < 0.05$ was taken as indicating a statistically significant difference.

Results

Sample Characteristics

Demographic and baseline clinical characteristics of the participants are presented on Table 1. Briefly, their age ranged from 25 to 68 years (mean = 47.12 ± 13.26 years). They had a mean of 5.14 ± 1.85 failed antidepressant trials and 2.15 ± 0.95 failed augmenting agent trials (e.g., lithium, atypical antipsychotics) in the current MDE. Mean baseline HAM-D_{21}, QIDS-SR_{16}, HAM-A, BAI, and CGI-S scores were 22.41 ± 5.94, 17.35 ± 4.14, 18.65 ± 8.39, 26.65 ± 13.10 and 5.53 ± 0.62, respectively, indicating moderate to severe overall symptomatology. The mean duration of the current MDE was 35.71 ± 24.33 months (ranging from 9 to 98 months). All patients were taking antidepressant medications at study entry (Table 2). Twelve participants (70.59%) had at least one Axis I comorbid disorder, and most patients (n = 13, 76.50%) had a severe TRD according to the MSM. Finally, the mean baseline and fourth week rMT estimates were, respectively, 62.2% ± 7.2% and 60.5% ± 6.9%.

Table 1

Table 2

Tolerability of the DTMS Treatment

Two of the 17 participants (11.76%) withdrew from the study at week 1 because of scalp discomfort during stimulation. Nevertheless, neither seizure nor other serious adverse events occurred out of the 306 daily DTMS sessions administered within this research protocol. Also, of the 15 study completers, only 2 (13.30%) reported significant side effects (mainly stimulation-related scalp discomfort) and thus required a temporary decrease in the initial intensity of stimulation. Finally, no participant had their dosage of benzodiazepine or non-benzodiazepine hypnotics changed during the trial because of treatment-emergent insomnia.

Pre-Post DTMS Outcome Measures

Table 3 provides a summary of the pre-post DTMS comparisons for the main outcome measures based on the intention-to-treat sample (n = 17).

Table 3

Clinical Measures

At study end, 12 (70.60%) patients responded to treatment and 7 (41.20%) remitted. Also, HAM-D_{21} and HAM-A scores were significantly reduced by week 5 as compared to baseline ($t = 7.44$, $p < 0.0001$, -48.87%, and $t = 4.82$, $p < 0.0001$, $\Delta = -50.60\%$, respectively). Moreover, there was a significant reduction in QIDS-SR_{16} ($t = 3.50$, $p = 0.003$, $\Delta = -25.24\%$), BAI ($t = 3.35$, $p = 0.004$, $\Delta = -18.07\%$) and CGI-S ($t = 6.06$, $p < 0.0001$, $\Delta = -30.56\%$) scores at study end. Hedges' *g* estimates for these clinical measures ranged from 0.6 (SSI) to 1.72 (HAM-D_{21}), i.e., medium to large effect sizes.

Quality of Life

There was a significant improvement in 4 of the 5 QOL domain scores from baseline to week 5: global ($t = -2.42$, $p = 0.028$), psychological ($t = -2.84$, $p = 0.012$), environmental ($t = -2.56$, $p = 0.021$) and social ($t = -3.85$, $p = 0.001$). The associated Hedges' *g* estimates ranged from 0.56 (global QOL) to 0.89 (social QOL), representing medium to large effect sizes. However, there was no significant change in the physical QOL domain ($t = -1.35$, $p = 0.19$).

Discussion

Our study has shown that DTMS was efficacious and relatively well tolerated for treating outpatients with severe TRD recruited from clinical practice. Response and remission rates at week 5 (based on the HAM-D_{21}) were 70.6% and 41.2%, respectively. Other measures (i.e., QIDS-SR_{16}, HAM-A, BAI, SSI and CGI-S) were also significantly improved at study end. Subjective QOL improvement has also occurred, as evidenced by significant increases in 4 of the 5 WHOQOL BREF domain scores (i.e., psychological, social, environmental and global QOL).

Tolerability of the DTMS Treatment

The high compliance rate observed in our study and the absence of serious adverse events suggest that DTMS treatment was relatively well tolerated. This is especially relevant considering that our stimulation protocol involved the delivery of almost twice as many magnetic pulses than previous DTMS studies in MDD (i.e., 3,000 vs. 1,680) (Rosenberg et al. 2010;Isserles et al. 2011). Furthermore, the compliance rate in our study is comparable to the rates reported by previous DTMS trials of the H1 coil for treating MDD (e.g., 82.6% in the initial feasibility trial (Levkovitz et al. 2010) and 78.9% in a more recent clinical trial (Isserles et al. 2011)). Nevertheless, the discontinuation rate associated with DTMS in our study was relatively higher than that observed in typical controlled trials of active rTMS in MDD (i.e., approximately 7.5% (Berlim et al. 2014)), although it is important to take into account our relatively small sample size and the preliminary nature of our findings. Clearly, head-to-head comparisons between DTMS and rTMS in terms of their potential differential acceptability are warranted.

Clinical Measures

The clinical results from our intention-to-treat analyses (n=17) compared favorably to those reported by the few previous trials of DTMS in TRD. For example, Rosenberg and collaborators (Rosenberg et al. 2010) have offered 20 daily sessions of DTMS to 7 drug-free depressed patients with TRD (i.e., lack of clinical improvement after ≥ 2 antidepressants of different pharmacological classes), and have shown that 3 (42.86%) responded to treatment and 1 (14.28%) remitted at study end. Also, Rosenberg and colleagues (Rosenberg et al. 2010) have reported, among 7 patients with TRD who had also failed to respond to a course of electroconvulsive therapy in the current MDE, that 4 weeks of daily DTMS treatment was associated with response and remission rates of 42.86% (n = 3) and 14.28% (n = 1), respectively. Taking these previous studies into consideration, one can hypothesize that the more intensive stimulation protocol employed in our trial might have

contributed to the relatively higher rates of response and remission observed (Gershon et al. 2003;Holtzheimer et al. 2010;Baeken et al. 2014). Also, the combination of our DTMS protocol with the ongoing antidepressant pharmacotherapy might have produced synergistic therapeutic effects and thus enhanced overall clinical effectiveness (Berlim et al. 2013). Nevertheless, both hypotheses need to be thoroughly tested in future studies.

Our main clinical findings also compare well to those reported by previous open label trials of HF-rTMS as an augmenting strategy for MDD. For example, in a recent large naturalistic study including 307 depressed outpatients treated with HF-rTMS for over 6 weeks, clinician-rated response and remission rates (based on the CGI-S) were 58% and 37.1%, respectively (Carpenter et al. 2012). Also, a retrospective 4- to 6-week open label trial of HF-rTMS adjunctive to medications in 85 patients with moderate TRD reported response and remission rates of 41.2% and 35.3%, respectively (Connolly et al. 2012).

Overall, the symptomatic improvement observed in our study is encouraging considering that the included patients had a severe and pervasive depressive illness. Furthermore, our results suggest that DTMS might be an efficacious adjunctive treatment even for depressed patients who present with negative baseline predictors of clinical response to HF-rTMS (e.g., longer duration of illness, presence of comorbid anxiety disorders) (Lisanby et al. 2009). Nevertheless, our findings are clearly preliminary and should be replicated by larger RCTs.

Quality of Life

There is a growing consensus in the literature that studies aiming at comprehensively measuring the benefits of treatments for MDD should also assess broader domains such as, for example, QOL (Kennedy et al. 2001;Demyttenaere et al. 2003;Papakostas et al. 2004). However, most previous trials on HF-rTMS and DTMS for MDD have not systematically assessed these alternative constructs. In the present study we showed that subjective QOL significantly improved

following DTMS treatment, and these findings are congruent with prior investigations on antidepressant pharmacotherapy (Skevington and Wright. 2001;Caliyurt and Gudücu. 2005;Berlim et al. 2007;Demyttenaere et al. 2008). Interestingly, the WHOQOL BREF evaluates aspects that are not usually covered by symptoms-based measures (Skevington et al. 2004). For example, its "social domain" includes items on satisfaction with personal relationships, social support, and sex life (Skevington. 2002). In summary, our preliminary results suggest that DTMS might not only relieve the core symptoms of MDD, but also positively affect other relevant psychosocial domains such as subjective QOL.

Limitations

Despite the encouraging results presented in this study, a number of limitations should be considered. Firstly, this was a relatively small open label trial as opposed to a blinded study, and treatment expectations of mental health practitioners, researchers and patients alike may have impacted the results (Brunoni and Fregni. 2011). Secondly, since we did not employ a control group, we could not estimate the impact of the placebo effect and/or of the natural course of MDD. There is, however, indirect evidence to suggest that the placebo response rates are significantly lower in subjects with TRD as compared to those with uncomplicated MDD (Dunner et al. 2006;Fekadu et al. 2009;Fournier et al. 2010). Thirdly, in our research protocol DTMS was given for 4 weeks, and perhaps a longer trial could have produced more robust clinical improvements (O'reardon et al. 2007). Fourthly, we only examined the immediate effectiveness of DTMS, and thus cannot estimate the stability of its medium- to long-term antidepressant effects. This is especially relevant considering the labor-intensive and time-consuming nature of DTMS. Although data remain somewhat limited in this regard, a recent small study has reported response and remission rates 3 months following a course of DTMS for MDD of 63% and 52%, respectively (n=12) (Levkovitz et al. 2010). Moreover, a 3-month continuation trial (n = 29) has shown that the

administration of DTMS following the acute treatment twice a week for 8 weeks and once a week for 10 more weeks was associated the probability of a sustained response and remission of 81.12% and 71.45%, respectively (Harel et al. 2012). Additionally, a second 4-week course of DTMS after a depressive relapse has been shown to significantly reduce depressive and anxious symptoms (n = 8) (Rosenberg et al. 2011). Fifthly, as the ability of the H coil to modulate deeper neuronal structures is obtained at the cost of a loss of focality (Zangen et al. 2005;Roth et al. 2007), it is possible that the relatively higher rates of clinical improvement observed in our study could have resulted from the larger brain volume receiving direct stimulation rather than from the depth of stimulation. Finally, we did not assess possible treatment-emergent behavioral activation secondary to the use of DTMS combined with psychotropic medications, and this issue should be explored in future studies.

Although recognizing these limitations, we argue that naturalistic studies like ours may assist in bridging findings from the evidence obtained with more narrowly defined patient populations to the anticipated effects of a treatment when used on a larger scale in more “real world” patients. In other words, we believe that both naturalistic and controlled designs are required to determine which therapeutic interventions are actually useful in daily clinical practice (Thase. 2001).

Conclusions

The present study suggests that 4 weeks of daily DTMS over the left DLPFC in patients with severe TRD is associated with clinically meaningful improvements in both depressive and anxious symptoms, as well as in subjective QOL. Overall, DTMS treatment was relatively well tolerated and was not associated with serious adverse events. However, further large RCTs are needed to better evaluate the clinical utility of DTMS as an augmenting strategy for TRD.

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Conflicts of Interest

Dr Berlim has received a researcher-initiated grant from Brainsway, Inc., to investigate, in a separate study, the neural basis of DTMS in MDD with the use of neuroimaging procedures. Dr Zangen is a consultant for and has financial interests in Brainsway, Inc. Drs. Chachamovich, Van den Eynde, Tovar-Perdomo and Turecki report no conflicts of interest.

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We received no direct funding for this study, although Brainsway, Inc., has provided us with a DTMS device.

Contributors

None.

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Table 1. Baseline demographic and clinical characteristics.

Characteristic	n	%	Mean ± SD
Gender			
Male	4	23.50	-
Female	13	76.50	-
Age (in years)	-	-	47.12 ± 13.26
Ethnicity			
Caucasian	16	94.10	-
Non-Caucasian	1	5.9	-
Schooling (in years)	-	-	15.24 ± 4.12
Depression history			
Lifetime MDEs	-	-	1.47 ± 1.42
Single episode	5	29.40	-
Recurrent	12	70.60	-
Current MDE			
Duration (in months)	-	-	35.71 ± 24.33
Failed antidepressants	-	-	5.14 ± 1.85
Failed augmenting agents	-	-	2.15 ± 0.94
Treatment-Resistance[a]			
Score	-	-	10.94 ± 1.85
Moderate	4	23.50	-
Severe	13	76.50	-
Axis I Comorbidity[b]			
Dysthymia	2	11.80	-
Panic Disorder	3	17.60	-
OCD	3	17.60	-
GAD	7	41.20	-

GAD = Generalized Anxiety Disorder; MDE = Major Depressive Episode; OCD = Obsessive-Compulsive Disorder.

[a] As indexed by the Maudsley Staging Method (Fekadu et al. J Clin Psychiatry 2009;70:177-84); [b] n=12 as the same patient could have had more than one psychiatric comorbidity.

Table 2. Participants' pharmacological regimen at baseline.

Participant	Medications (daily dosages)
1	Sertraline 200 mg + bupropion XL 450 mg + clonazepam 1 mg
2	Nortiptyline 75 mg + sertraline 125 mg + quetiapine 50 mg
3	Bupropion XL 300 mg + buspirone 60 mg
4	Sertraline 150 mg + ritalin SR 72 mg
5	Escitalopram 30 mg + nortriptyline 100 mg + lorazepam 1.5 mg
6	Desvenlafaxine 100 mg + bupropion XL 450 mg
7	Mirtazapine 45 mg + venlafaxine 300 mg + lorazepam 2 mg
8	Citalopram 40 mg + bupropion XL 300 mg + olanzapine 5 mg
9	Venlafaxine 375 mg + pramipexole 1 mg + quetiapine 100 mg
10	Bupropion XL 450 mg + citalopram 60 mg + olanzapine 7.5 mg
11	Tranylcipromine 50 mg + clonazepam 2 mg
12	Duloxetine 120 mg + aripiprazole 10 mg
13	Paroxetine 40 mg + mirtazapine 30 mg
14	Escitalopram 20 mg + bupropion XL 450 mg + quetiapine 150 mg
15	Bupropion XL 450 mg + aripiprazole 5 mg
16	Duloxetine 90 mg + bupropion XL 300 mg
17	Venlafaxine 375 mg + lithium carbonate 900 mg + quetiapine 100 mg

Table 3. Pre-post DTMS comparisons for the main outcome measures (n=17).

Variable	Mean ± SD	t	df	p	Hedges' *g*
HAM-D_{21}		7.44	16	< 0.0001	1.72[a]
Pre	22.41 ± 5.94				
Post	11.00 ± 4.54				
QIDS-SR		3.50	16	0.003	0.81[a]
Pre	17.35 ± 4.14				
Post	12.65 ± 6.15				
CGI-S		6.06	16	< 0.0001	1.40[a]
Pre	5.53 ± 0.62				
Post	3.82 ± 1.13				
HAM-A		4.82	16	< 0.0001	1.11[a]
Pre	18.65 ± 8.39				
Post	8.59 ± 4.95				
BAI		3.35	16	0.004	0.77[b]
Pre	26.65 ± 13.10				
Post	20.53 ± 13.07				
SSI		2.60	16	0.019	0.60[b]
Pre	10.88 ± 9.25				
Post	8.12 ± 9.41				
WHOQOL BREF – Physical		-1.35	16	0.19	NS[c]
Pre	34.87 ± 18.45				
Post	37.99 ± 16.42				
WHOQOL BREF – Psychological		-2.84	16	0.012	0.65[b]
Pre	32.60 ± 20.16				
Post	40.19 ± 18.45				
WHOQOL BREF – Social		-3.85	16	0.001	0.89[a]
Pre	34.80 ± 14.58				
Post	47.62 ± 15.62				
WHOQOL BREF – Environmental		-2.56	16	0.021	0.59[b]
Pre	55.94 ± 17.04				
Post	61.33 ± 15.09				
WHOQOL BREF – Global		-2.42	16	0.028	0.56[b]
Pre	37.13 ± 24.82				
Post	47.79 ± 19.38				

BAI = Beck Anxiety Inventory; CGI-S = Clinical Global Impression – Severity Subscale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D_{21} = 21-item Hamilton Depression Rating Scale; QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology – Self-Report; SSI = Scale for Suicidal Ideation; WHOQOL BREF = World Health Organization's Quality of Life Measure – Brief Version.
[a] Large effect size; [b] Medium effect size; [c] No effect size was calculated because the difference between pre-post DTMS scores was not statistically significant.

Figure 1. Percentage score changes post-DTMS on the HAM-D_{21} and the HAM-A.

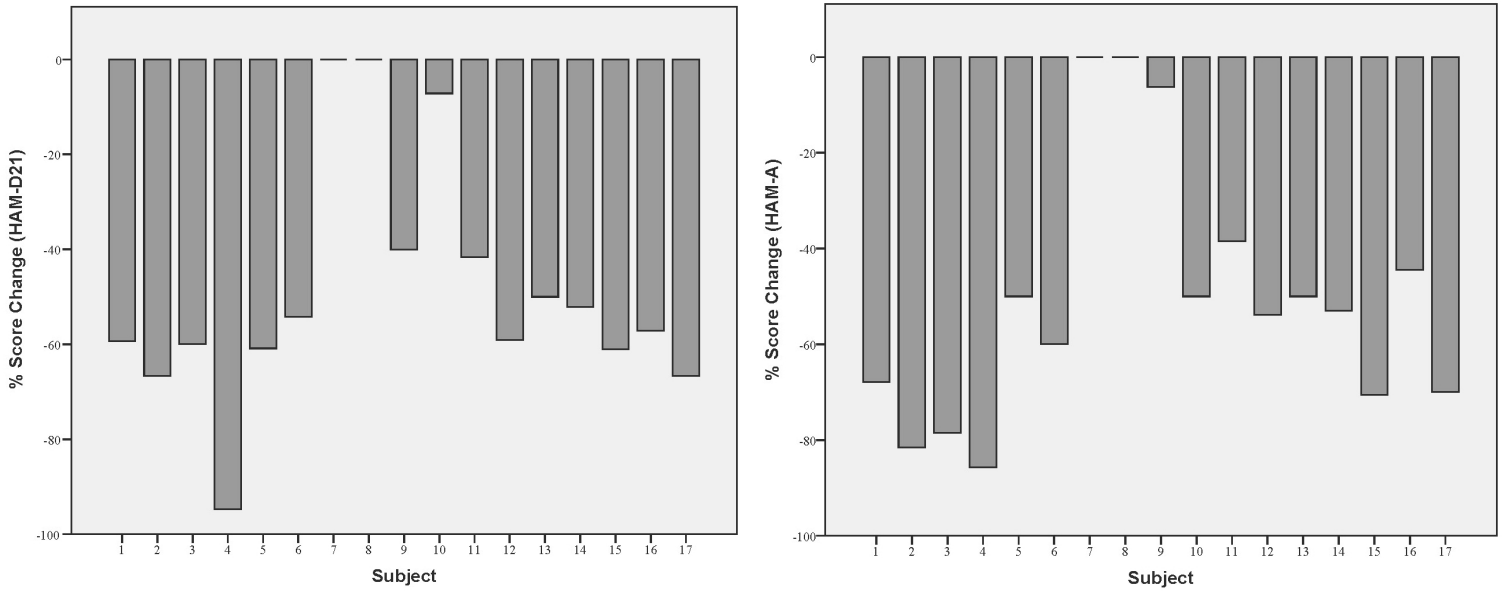
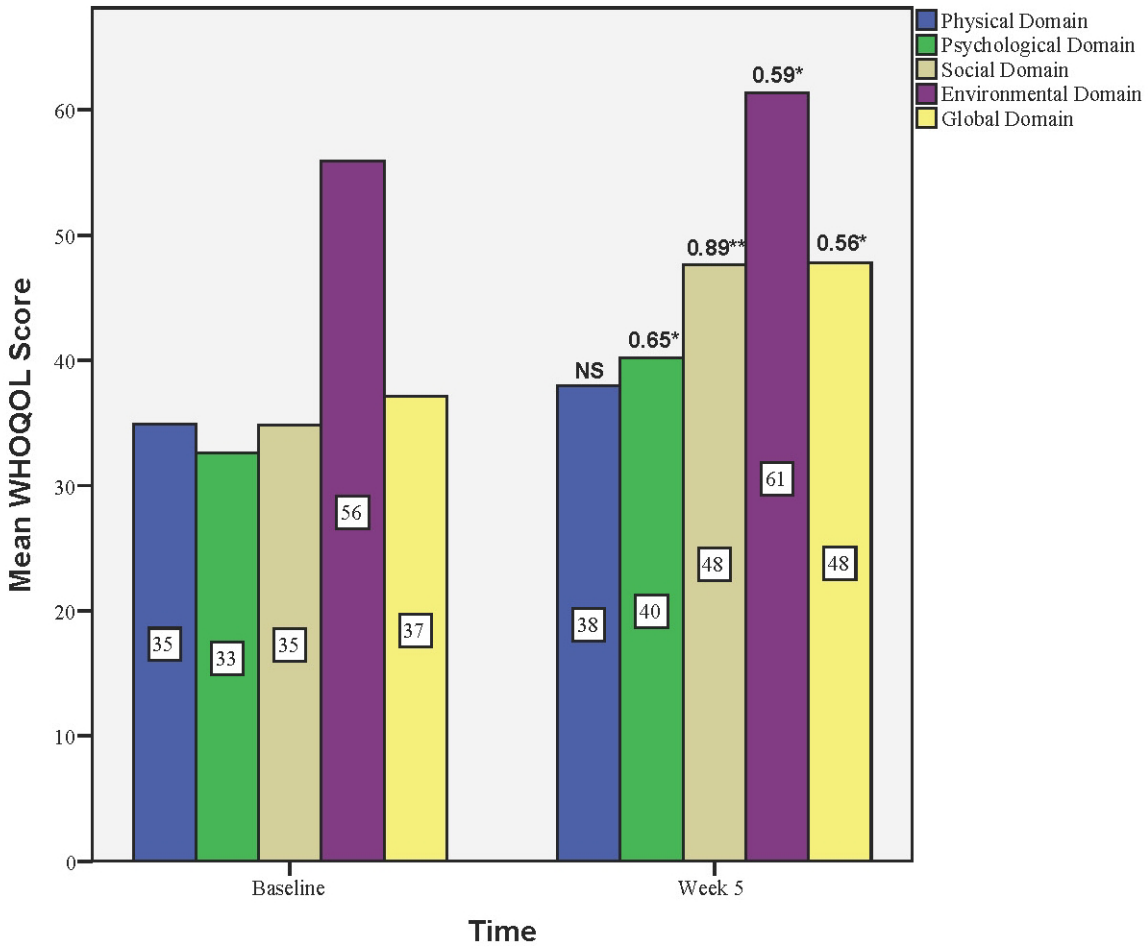


Figure 2. Quality of life domains: score changes and Hedges' *g* effect sizes pre-post DTMS.



NS = Non-significant; * Medium-sized Hedges' g; ** Large-size Hedges' g