Original Article

Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder: Preliminary Results from the United Arab Emirates

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Abstract

Background: Despite evidence for its efficacy, the use of repetitive transcranial magnetic stimulation (rTMS) to treat major depressive disorder (MDD) remains limited in the Middle East and North Africa. The following study evaluated the efficacy of this therapy on patients diagnosed with MDD attending the Outpatient Clinic at the American Center for Psychiatry and Neurology in Abu Dhabi, United Arab Emirates. Methods: Thirty-three patients with treatment-resistant MDD were treated with rTMS according to the Food and Drug Administration (FDA)-approved protocol. The patients received five treatment sessions per week over a period of 4–6 weeks, and they completed the Patient Health Questionnaire (PHQ-9) before and after the treatment course. Results: We observed a 58% response rate to treatment, with a 30% remission rate of depressive symptoms, consistent with previous studies. Limitations: Our results do not reflect long-term efficacy of rTMS, as post-therapy scores were obtained immediately after treatment. Although significant, the reduction in PHQ-9 scores cannot be generalised due to the relatively small sample size. Future studies could look into specific characteristics of patients for better profiling of rTMS candidates. Conclusion: An FDA-approved protocol involving five weekly sessions of rTMS over the dorsolateral prefrontal cortex was effective in treating MDD. Our secondary finding of lower acceptability rate among patients may indicate the need for shortened treatment duration and comprehensive insurance plans providing coverage for rTMS therapy.

Keywords: Dorsolateral prefrontal cortex, major depressive disorder, Middle East and North Africa, neuromodulation therapy, repetitive transcranial magnetic stimulation, United Arab Emirates

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INTRODUCTION

Affecting more than 350 million people of the world’s population, depression is the fourth leading contributor to the global burden of disease. Major depressive disorder (MDD) is an episodic mood disorder that is characterised by the sustained presence of depressed mood and anhedonia. MDD is associated with severe functional impairment and affects sleep and appetite, significantly reducing the patients’ quality of life. Primarily, pharmacological therapies are used to treat and manage MDD, but their efficacy has been undermined by low remission rates, undesirable side effects and intolerance to certain medications. While less effective than pharmacotherapy alone, psychotherapy has been demonstrated to improve outcomes when combined with antidepressants and may be effective in managing treatment-resistant depression. However, effect sizes have been small and psychotherapy has been criticised for its long duration of treatment and its inability to produce long-lasting remission.

Alternatively, neuromodulation therapies are typically used when patients do not respond to standard treatment options such as pharmacological treatments or psychotherapy. In some cases, neuromodulation therapies are concomitantly given to patients receiving both forms of therapy. To date, the most effective neuromodulation therapy for MDD has been electroconvulsive therapy (ECT), but its invasive nature and significant side effects have limited its widespread use.

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use. Approved for clinical use by the Food and Drug Administration (FDA) in 2008, transcranial magnetic stimulation (TMS) is a relatively novel technique that uses brief electrical currents, delivered to a coil to induce a magnetic field, that when applied to the skull, is able to modulate brain activity. Repetitive TMS (rTMS) pulses over the dorsolateral prefrontal cortex (DLPFC) have been shown to produce antidepressant effects, possibly due to the involvement of this area of the brain in mood regulation. It is found that rTMS has many benefits over ECT, most notably that it is non-invasive, safe, can be conducted in an outpatient clinic setting and does not have the systemic side-effects associated with antidepressants that lead patients to discontinue treatment. Treatments using rTMS have also been successful in treating patients with migraine and gait dysfunction in vascular parkinsonism. rTMS has been included as a potential treatment option for treatment-resistant depression by the National Institute for Health and Care Excellence guidelines as well as the American Psychiatric Association guidelines.

Randomised clinical trials have demonstrated the superiority of rTMS over the left DLPFC to sham conditions. Furthermore, studies suggest a 30%-50% remission rate that is maintained for up to 5 months after ending the treatment course. In a systematic review of studies that were carried out on the efficacy of rTMS, Gross et al. found larger antidepressant effects were found in recent rTMS clinical trials when compared with the findings of previous studies. Evidently, current rTMS clinical trials use novel parameters of stimulation such as varying the sight and frequency of stimulation from either a single sight stimulation over the right DLPFC with low frequency or the left DLPFC with high frequency (HF) or bilateral stimulation. They also had larger sample sizes and improved study designs. In addition, a meta-analysis done by Berlim et al. concluded that patients with MDD respond well to bilateral rTMS treatment.

Despite the wealth of evidence and support for rTMS, its use remains limited in many parts of the world, including the United Arab Emirates (UAE). Around 5.1% of the UAE population is said to suffer from a type of depression. In an epidemiological survey of help-seeking behaviors among patients in Al-Ain, 44.8% were reported to seek non-professional help for psychiatric disorders before attending specialised services. These include consulting traditional and faith healers to treat illnesses such as depression. Nonetheless, in the years between January 2010 and May 2013, 8.6% of patients visiting a neuropsychiatric clinic in Abu Dhabi were treated for clinical depression. Widely used treatment options remain to be traditional healing methods, pharmacological therapies and psychotherapy and rTMS as a form of treatment for MDD is relatively new. This clinical study describes the results of using NeuroStar rTMS therapy to treat patients with MDD at a private neuropsychiatric clinic in the UAE. Clinical response and remission rates are reported, as well as pre-post changes in depressive symptoms based on the nine-item Patient Health Questionnaire (PHQ-9).

**Methods**

This study was approved by the Institutional Review Board at the American Center for Psychiatry and Neurology (ACPN), Abu Dhabi, UAE (Reference number: ACPN-IRB-PN-0016). Of the initial 45 patients, eight discontinued treatment before completing the minimum required 20 sessions and four were still receiving treatment at the time of data extraction. For this trial, 33 patients were included. Patients were recruited between February 2013 and December 2015 from the Department of Psychiatry at ACPN, and written informed consent to treatment was solicited from each patient. Medical, psychiatric, contraindication and safety screenings were performed by the treating psychiatrists and a trained mental health nurse as per the standards detailed in the NeuroStar TMS Therapy System User Manual, 52-40020-100 Revision B. Any patient who did not meet the set criteria was excluded from the study. Baseline laboratory tests were carried out only if recommended by the attending psychiatrist and depending on each patient’s medical history. These include urine toxicology screening and electrocardiography following standard clinical procedure.

**Patients**

Patients 18 years of age and older meeting the following criteria were included in the study: diagnosis of MDD without psychotic features, consistent with DSM-IV TR criteria/ICD-9 codes (296.22, 296.31, 296.32, 296.33, 300.4 and 311), no history of manic episodes, inadequate response to antidepressant treatment and/or psychotherapy, inability to tolerate medications or interest in non-drug treatment for depression, failure to respond or tolerate at least one treatment in the current depression episode and no contraindication to rTMS. The data presented here are for patients who have completed the nine-item (PHQ-9) before and at the end of treatment ($n = 33$; male/female = 15/18; age mean = 40.6, standard deviation [SD] ±11.9 years). The average duration of depression prior to treatment was 13 years (minimum =2 years, maximum =40 years). The minimum age of onset for this cohort was reported as 13 years. Sixteen patients were taking antidepressants only and six patients were receiving psychotherapy as well as antidepressants. 27.3% were taking two types of medication, while 39.4% were on one type of medication prior to receiving treatment. In this study, we defined responders as patients who scored <9 on the PHQ-9 post-rTMS treatment, indicating improvement, and remitters as those who scored <4 post-treatment.

**Instruments**

The PHQ-9 is a nine-item self-administered questionnaire used to screen and diagnose depression. It has been credited for its sensitivity to detect changes in depressive symptoms over time and is based on the nine DSM-IV criteria for depression. A total score of >10 indicates the presence of depression. It has been validated for use on the general population. Both the English and Arabic versions were used.
Treatment procedure
The NeuroStar® TMS Therapy System (Neuronetics, Inc., Malvern, PA, USA) was used for treatment. The standard FDA-approved treatment protocol as described in Horvath et al. was administered to patients. The study followed safety and tolerability measures detailed out in the NeuroStar TMS Therapy System user manual, 52-40020-000 Revision D, pages 2-3, 2-4 and 2-5. HF stimulation (10 Hz) was delivered over the left DLPFC, which was determined by movement of the TMS coil 5.5–6 cm anterior to the motor threshold location along a left superior oblique plane. This was done at 120% of resting motor threshold, 4 s of active stimulation followed by 26 s of no stimulation for a total of 3000 pulses per treatment session. Patients received a minimum of 20 sessions, with five sessions per week, for a duration of 4–6 weeks. The rTMS was administered by a trained nurse, with weekly follow-ups with the treating psychiatrists. The nurse followed up with patients 1–2 weeks after completion of treatment and booked a follow-up consultation with the treating specialist at 3 months after completing treatment.

Statistical analysis
Statistical Package for the Social Sciences, Version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used to conduct statistical analysis. A paired-sample t-test was performed on PHQ-9 scores and descriptive analyses were then done on these scores to determine remission rates (post-rTMS score ≤4), response rates (post-rTMS score ≤9) and non-response rates (post-rTMS score >9). Follow-up correlational analyses were done to determine whether the change in PHQ-9 scores was associated with other variables. Repeated-measures analysis of variance (ANOVA) was performed to determine whether concurrent treatment influenced change in scores.

RESULTS
A description of the sample’s characteristics is described in Table 1. The paired-sample t-test revealed a significant reduction in PHQ-9 scores at the end of the rTMS course (pre: 17.9 ± 4.9, post: 8.7 ± 6.6; \( t = 7.866, P < 0.001, d = 1.369 \)). Table 2 describes remission, response and non-response rates. A total of 58% of the sample responded to the rTMS treatment, with an average of 75% reduction in depression scores. Specifically, 30% had remitted with an average of 86% reduction in depression scores, while 42% did not respond.

Change in PHQ-9 scores did not correlate with age, duration of illness or number of rTMS sessions, but correlated significantly with the initial PHQ-9 score \( (r^{20} = 0.391, P = 0.024) \), suggesting that more severe depression was associated with greater reduction in scores at the end of treatment. The repeated-measures ANOVA on the effect of concurrent treatment on the effect of therapy revealed a significant interaction \((F [3, 29] = 3.252, P = 0.036)\). Post hoc analysis revealed that the reduction in PHQ-9 scores was significant for the following groups: rTMS alone \((F [1, 9] = 20.328, P = 0.001)\) and rTMS + antidepressants \((F [1, 15] = 56.971, P < 0.001)\). A one-way ANOVA showed no statistical difference in response to treatment between the three treatment groups, \((F [3, 29] = 1.199, P = 0.327)\). Patients on antidepressants \((mean = 1.43, SD = 0.51)\) did not differ in their treatment outcome from patients who were receiving both antidepressants and psychotherapy \((M = 1.17, SD = 0.41)\), as well as those on no other forms of treatment outside rTMS \((M = 1.60, SD = 0.52)\).

Discussion
We presented data on the clinical outcome of rTMS, delivered to 33 patients over the DLPFC for a minimum of 20 sessions,
five times a week, for 4–6 weeks. Our findings are in agreement with previous reports of rTMS efficacy with 58% response rate to treatment and 30% remission rate of depressive symptoms. Reported adverse effects included minor headache which was most commonly reported among patients, and insomnia, less commonly reported. These symptoms resolved on their own and did not lead to treatment discontinuation. Temporary discomfort was also noted in few patients during treatment where vibration around the right lower teeth was reported, which was then alleviated upon adjusting the position of the coil. The registered nurse followed up with the patients between 1 and 2 weeks after completing 4–6 weeks of treatment, and on average, symptoms improved around the 20th session mark.

An important finding from this study is the acceptability rate of rTMS among patients. Of the initial 45 registered patients, 33 (73%) completed the full duration of treatment, while four (9%) were still in treatment at the time of data compilation, and eight patients (18%) discontinued treatment after attending a minimum of five and a maximum of 17 sessions. The dropout rate for this study was significantly higher than studies with similar treatment duration and clinical outcome, which had a dropout rate of just 7%. It was understood that potential reasons for dropping out for our cohort included length of time and cost of treatment. There is new evidence that patients are more likely to complete treatment when treatment duration is shortened; McGirr et al. looked at the efficacy of an accelerated protocol of HF-rTMS applied over the DLPFC, twice-daily for two consecutive weeks. The results showed 56% response rate and 37% clinical remission, as well as a 0% dropout rate (n = 27). A more recent finding also showed 35% of patients with refractory MDD responded to accelerated HF rTMS where patients received multiple daily sessions of a HF-rTMS over the dorsomedial prefrontal cortex as opposed to the classical single daily rTMS sessions spread across a 2–4 weeks period. They argued the accelerated treatment shortened the treatment duration from the depressed state to the response state and also reduced the total treatment period to just over a couple of days. As a relatively novel approach to treating depression, shortening treatment duration may be one of way improving acceptability rate among patients.

In addition, multicenter studies show that rTMS is the least cost-effective treatment when compared with other neuromodulation therapies such as ECT. Hamidi et al. argue that there the usage of psychiatric service in the UAE may best be explained by applicable costs and the extent to which insurance plans cover such costs. They found 36% of the total costs on ambulatory neuropsychiatric services were paid directly by patients. Their study calls on policy-makers to regulate health insurance plans to cover neuropsychiatric services. We argue that the acceptability rate for rTMS would increase in cases where patients have comprehensive health insurance plans. Our study serves as a preliminary evidence to corroborate our findings on a larger scale. More clinical studies are needed to validate long-term efficacy and generalisability of our results, and that given apparent effectiveness of the treatment, efforts should be made to increase accessibility.

**Limitations**

This was a pilot study, and as such, comes with certain limitations that we hope we will address and rectify in subsequent trials. Data for this study were collected routinely from regular treatment sessions of outpatients at the clinic upon soliciting their consent. As a result, the study protocol did not include a sham control group. We hope to address this in subsequent trials with better research design and methodology. Based on the previous findings, measuring treatment outcomes at five-session intervals as opposed to at the end of the treatment period would have enhanced our results, which we hope to introduce in subsequent trials. Furthermore, as measures were administered at the end of the last rTMS sessions, results reflect an immediate effect of the therapy and follow-up is required to determine whether effects persist over time. Similar to our study, several studies suggest rTMS as an augmentative treatment to antidepressants. Although still significant, the reduction in scores in the group on rTMS alone was smaller. That said, the generalisability is precluded by the small sample size. Additional data are needed to investigate the insignificant reduction in scores seen in the group on both antidepressants and psychotherapy. Future studies could investigate the presence of specific characteristics that differentiate those who responded to rTMS from those who did not, in an effort to profile the right candidates for this promising therapy for MDD.

**Conclusion**

Consistent with previous reports, significant reductions in depressive symptoms were observed after a minimum of 20 rTMS sessions in patients with treatment-resistant depression. Almost a third of the sample achieved remission which was indicated by an average of 86% reduction in PHQ-9 scores. Together, these results suggest that a course of rTMS pulses over 5 days for 4–6 weeks is a promising treatment option for patients with MDD who are unable to benefit from other alternatives.

**Ethical statement**

This study was approved by the Institutional Review Board at the American Center for Psychiatry and Neurology (ACPN), Abu Dhabi, UAE (Reference number: ACPN-IRB-PN-0016).

**Declaration of patient consent**

The authors certify that they have obtained written patient/participant consent. The patients have given their consent for their clinical information and any data to be reported in the journal. The patient/participant understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.
Conflicts of interest
There are no conflicts of interest.

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