Repetitive transcranial magnetic stimulation (rTMS) using different TMS instruments for major depressive disorder at a suburban tertiary clinic

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a neurostimulatory technique used to modulate orbital frontal corticostriatal (OFC) activity and clinical symptomatology for psychiatric disorders involving OFC dysfunction. We examined the effectiveness of rTMS in the treatment of major depressive disorder in an applied clinical setting (Awakening KC CNI) to assess efficacy and optimize rTMS parameters within clinical practice. A retrospective review of medical records was carried out on patients with major depressive disorder undergoing rTMS therapy at Awakenings KC Clinical Neuroscience Institute (CNI), a suburban tertiary psychiatric clinic. A detailed de-identified data set of clinical outcomes was compiled. Patient Health Questionnaire 9 (PHQ-9) total score, clinical remission rate and week achieved were evaluated over 6 weeks of treatment to assess clinical response referencing two different rTMS instruments (MagVenture; NeuroStar). Our survey included 247 participants from males (N=98) and females (N=149) with average baseline PHQ-9 scores of 21.7±4, classified as *severe depression*. Clinically rated remission rates of 72% were achieved in 3.1±1.0 weeks and associated with prior history of psychiatric hospitalization, suicide attempts and substance use disorder. Average baseline PHQ-9 scores decreased significantly over time with proportionately greater remission rates achieved for patients treated using the MagVenture over NeuroStar instrument. rTMS in applied clinical practice is efficacious over a wide range of settings and patients. Clinical response was related to severity of depression symptoms (*e.g.,* prior hospitalization; suicide attempts) validating efficacy in critically ill groups. Clinical response may be impacted by rTMS instrument, magnetic field parameters or individual factors.

Introduction

Major Depressive Disorder (MDD) has a complex etiology with neurobiological deregulation of cellular signaling involving select brain regions and neurotransmitter systems (Knowland and Lim;[1] Post and Warden[2] for reviews). The regulation of mood can be influenced by the activity of the orbital frontal corticostriatal (OFC) circuits involving the medial prefrontal cortex (mPFC), the hippocampus, the limbic system, amygdala, and other regions identified and characterized using Neuroimaging and other technology. Some brain regions have been found to be hyperactive such as the anterior cingulate cortex, while others are hypoactive, such as the prefrontal cortex, hippocampus and thalamus. Disturbances in several specific neurotransmitters [*e.g.*, serotonin (5-HT), dopamine (DA), and norepinephrine (NE)] have been associated with MDD diagnosis and reports of depressive symptoms.[1] These systems are targeted by medications that treat MDD which modulate their activity at the synaptic level. Kessler *et al*.[3] found approximately 14 million adults meeting the diagnostic criteria for Major Depressive Disorder (MDD) with only half receiving treatment. Of the estimated 7.2 million adults with MDD that did receive treatment, four million reported feeling dissatisfied with the treatment they engage in. According to a 2017 report from the National Institute of Mental Health, approximately 16.2 million adults (6.7% of adults) reported at least one depressive episode in the last year emphasizing the need for an alternative treatment method for MDD (https://www.nimh.nih.gov/health/statistics/major-depression.shtml).

Repetitive Transcranial Magnetic Stimulation (rTMS) was developed and optimized to target and modulate prefrontal cortical activity and regulatory feedback pathways involved in depression, and is often used for refractory depression delineated by subjective symptoms. In TMS, the application of a magnetic field perpendicular to the brain generates an electric field parallel to the neurons leading to changes in the electrical membrane potential of the neurons and increased activity.[4,5] Barker *et al*.[6] developed the TMS machine in the 1980s with the ability to depolarize neurons up to 2 cm deep in the brain.[6,7] Repetitive stimulation of targeted brain regions was found to yield longer lasting effects at the neuronal level. Lefaucheur *et al*.[8] confirmed that rTMS treatment can affect neurotransmitter systems, regrowth of nervous tissue in the brain, and excitability from cortical regions of the brain. Pascual-Leone *et al*.[9] tested the efficacy of rTMS on the left DLPFC of patients with medication-resistant MDD finding significant improvement in depressive symptoms and adding to the literature supporting rTMS as a safe treatment in alleviating depressive symptoms in a clinical setting. George *et al*.[10] reported significantly greater antidepressant effects compared to sham with remission rates of 30% after 3 to 6 weeks of rTMS treatment. Subsequent studies indicate that psychiatric disorders related to OFC dysfunction can be modulated using neurostimulatory techniques such as rTMS and transcranial direct current stimulation (tDCS) to elicit changes in corticostriatal activity impacting clinical symptomatology.[5,11-16] Slotema *et al*.[17] analyzed 34 FDA approved Large-Scale Randomized Controlled Trials (RCT's), totaling over 1300 patients, with an effect size of .55 and found rTMS was more effective than the sham treatments with a moderate mean effect on depressive symptoms. As TMS treatment became increasingly utilized in treating depression, safety guidelines have been developed to safe guard against potential seizures and other health risks.[18-22]

The application of rTMS to the treatment of psychiatric illness remains widely utilized in research settings with few reports of the practical application to ethnically, financially, and geographically diverse patient groups with complex comorbidities.[23-25] Huber *et al*.[23] evaluated gender in the effect of rTMS

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Key words: TMS, rTMS, transcranial magnetic stimulation, depression, treatment, remission.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received for publication: 22 November 2018.
Accepted for publication: 22 November 2018.

Licensee PAGEPress, Italy
Mental Illness 2019; 11:7947
doi:10.4081/mi.2019.7947

and failed to identify differences in the clinical outcomes. Pallanti *et al*.[26] reported a significant inverse relationship between rTMS treatment response and age in men over 60 years of age but not for younger men. Inconsistent reports support synergistic effects of rTMS and Cognitive Behavioral Therapy (CBT) treatment on remission rates in MDD. However, there is limited information regarding these techniques as applied in general clinical practice. Systematic examination of clinical outcomes and impact of well-defined treatment groups in practical applied clinical setting will advance understanding of the safety and efficacy of rTMS alone and in combination with CBT for MDD with co-morbidities to help optimize protocol and define exploratory outcomes. We evaluated the effectiveness of rTMS and CBT combined with rTMS in the treatment of MDD and other related psychiatric co-morbidities and conditions in an applied clinical setting (AwakeningsKC, CNI). The study aim was to provide preliminary data to assess efficacy and optimize rTMS parameters within clinical practice, expand rTMS application to other psychiatric conditions, and observe the effect of rTMS on patients comorbidly diagnosed with other disorders.

Methods and Materials

AwakeningsKC Clinical Neuroscience Institute

AwakeningsKC CNI is a tertiary health care center for outpatient psychiatric treatment located in Prairie Village, Kansas. The facility has three clinics for Medication-Psychotherapy, repetitive Transcranial Magnetic Stimulation (rTMS), and intensive outpatient Cognitive Behavioral Therapy (CBT). The Medication-Psychotherapy clinic is the most often utilized and is commonly the referral source for the rTMS and CBT clinics based upon assessed patient needs. AwakeningsKC CNI is a Kansas State Certified facility for CBT consisting of 12-18 psychotherapy sessions for three hours, three times a week administered by licensed clinical social workers. New patients are initially evaluated by a psychiatrist who develops a treatment plan encompassing psychotropic medications and/or psychotherapy and assesses their candidacy for rTMS.

Repetitive Transcranial Magnetic Stimulation Instruments

AwakeningsKC CNI has applied clinical data utilizing two different rTMS stimulators, MagVita (MagVenture, Alpharetta, GA) and NeuroStar (Neuronetics, Malvern, PN).[27] Both instruments utilize a magnetic coil with a figure eight configuration for optimal focus of stimulation.[28] The MagVenture utilizes a Cool B65 Butterfly Coil with a 280 μs pulse width and includes a dynamic liquid cooling system to prevent overheating in repeated applications. The NeuroStar utilizes an Iron (ferromagnetic) Core Figure Eight Coil which generates less heat but has no cooling mechanism. The NeuroStar instrument has a 185 us pulse width, narrower than the MagVenture, leading to increased reports of side effects due to sharp and painful sensations at the site of application. All TMS machines also produce an auditory clicking or tapping sound resulting from vibration generated from the electromagnetic force of the repeated pulses. The standard FDA approved protocol for the NeuroStar emits a 93.9 dB acoustic output based on 100% machine output (MO) and 10Hz stimulation frequency. MagVenture's acoustic output at 100% MO is lower than NeuroStar instrument but is still estimated to be 83.4 dB; thus, all patients were advised to wear earplugs for protection.

Repetitive Transcranial Magnetic Stimulation Parameters

rTMS treatments were administered by psychiatrists or trained technicians closely overseen by an MD. The standard rTMS treatment protocol consisted of a single daily 37-minute session over a period of 6 weeks up to a maximum of 30 treatments. Treatment sessions were carried out in a sequestered room with an adjustable chair and a large screen television where patients were able to select viewing from Netflix, Hulu, YouTube, or music of their choice. The patients were advised to wear earplugs during the treatment. Individual treatment times and instruments were applied consistently to maximize outcomes.

The motor threshold (MT) was defined based upon the activation of the Abductor Pollicis Brevis (APB) motor cortex after the coil was positioned on the dorsolateral prefrontal cortex, located approximately 2.2 inches below the center line of the head on the interauricular line from the ear through the center of the head at the top. MT mapping using the NeuroStar system was a semi-automated process while the MagVenture instrument was carried out manually based upon measurements of the scalp.[27] The MT was identified for each patient prior to treatment and re-assessed weekly throughout the treatment phase.

Data Collection

This study was conducted under the authority of the University of Kansas Medical Center Office of Research Compliance who reviewed the study protocol and monitored study activities to ensure that appropriate steps were taken to protect the rights and welfare of humans participating as research subjects. Electronic medical records (Bestnotes, Twinfalls, ID) from patients of AwakeningsKC CNI were searched to identify adult men and women aged 18-80 years with Major Depressive Disorder who received up to 6 weeks of rTMS treatment as a component of their psychiatric treatment for depression. PHQ-9 scores and clinician rated clinical response determinations were collected with medical, psychiatric and family history and demographics including age, sex, education, socio-economic status, marital status, and employment.

Study Assessments

The following study assessments were routinely collected as part of patient surveillance and monitoring.

Initial Intake Assessment Form: All clinic patients completed an 11-page downloadable assessment form prior to their initial intake visit. This form included self-reported patient demographic information, detailed substance abuse history, psychiatric self-assessment, past psychiatric treatment, medical history, current and past medications, family medical history, and family psychiatric history. Patient Health Questionnaire (PHQ-9): The PHQ-9 is a validated 9-item self-report questionnaire that assesses depression symptoms summarized from the DSM criteria for MDD. Items are scored from "0" (not at all) to "3" (nearly every day) with a maximum total score of 27. PHQ-9 has a diagnostic sensitivity of 97% and specificity of 67% and scores aide in monitoring depression severity and response to treatment over time.[29-31] Remission is reached when a PHQ-9 score less than 5 is achieved. A PHQ-9 score less than 50% of baseline is considered clinically significant improvement.

Clinician-Defined Remission Rates: The clinician defined remission was based on changes in depressive symptomology, such as noted interest in activities, feelings of hope and positivity for the future, improved sleeping and appetite disturbances, a presence of volition in the patient's speech, an improved self-esteem, improved cognitions, improved lethargy, and presentation of brighter affect.

TMS Adult Safety Screen (TASS): The TASS is a 13-item standard screening questionnaire for neurological disturbances that may be contraindicated in TMS to safeguard against potential negative reactions.

Items query a myriad of physical issues such as trauma, seizure, cardiovascular history; hearing problems or implanted devices.[32,33]

Data Analysis

SAS statistical software version 9.4 (SAS Institute Inc. Cary, North Carolina, USA) was used for all data analyses. Summary statistics were generated to describe baseline characteristics (Table 1). Chi Squared test was applied for bivariate analyses with Cochran-Mantel-Haenszel and Breslow-Day tests of common odds ratios to identify significant co-variants impacting the frequency of clinical remission from depression. Repeated measures MANOVA was used to evaluate changes in PHQ-9 scores and independent effects on clinical response over the 6-week treatment period. Stepwise logistic regression modeling was applied to the identified co-variates to develop a parsimonious model of clinical response to rTMS therapy based upon the frequency of clinician rated remission.

Results

We identified 247 adult men (N= 98) and women (N=149) from the electronic medical records at AwakeningsKC CNI experiencing up to 6 weeks of rTMS therapy. The sample had a mean age of 42.9±13.9 years (range: 18 to 78 years; Table 1). The sample was about 60% female and predominantly Caucasian (97%) with high rates of prior psychiatric hospitalization (62%) and previous suicide attempts (36%). The majority (67%) reported a family history of MDD among first degree relatives and/or grandparents. Average PHQ-9 score at baseline was 21.7±4 classified as *severe depression* which did not differ by gender, prior suicide attempt or inpatient psychiatric hospitalization. Males were significantly more likely to report a history of substance use than females and females had higher rates of CBT combined with rTMS. rTMS did not preclude the use of psychiatric medications which varied in our analyses with no differences noted between groups.

Clinician-Defined Remission Rates

The clinician defined remission was based on changes in depressive symptomology, such as noted interest in activities, feelings of hope and positivity for the future assessed independently of psychometric measures. The overall rate of clinical remission as indicated by clinician rating of depression symptoms was 72% achieved after 3.1±1.0 weeks of rTMS (Table 2) which did not differ by sex. Statistically significant increases in clinical response rates were identified for patients with prior history of psychiatric hospitalization ($\chi^{2=}$ 7.9, P=0.005), prior suicide attempts ($\chi^{2=}$ 4.8, P=0.03) and history of substance use ($\chi^{2=}$ 5.6, P=0.02). Seventy-eight percent (N=120) of individuals with a prior history of psychiatric hospitalization achieved remission compared to sixty-one percent (N=57) of those without prior hospitalization. Similarly, eighty percent (N=72) of those reporting a prior suicide attempt achieved remission compared to sixty-seven percent (N=105) of those not reporting suicide attempts. Ninety percent (N=27) of those with an SUD achieved remission compared to sixty-seven percent (N=105) of those without and SUD. All of the nine women with a duel diagnosis of MDD and SUD achieved remission from their depression. In addition, patient age was correlated with increased number of weeks to achieve clinical remission (t=2.1, P<0.04). A statistical trend was observed in clinical remission rates for patients meeting criteria for obesity status (87%, BMI>30) according to height and weight measurements compared to those not meeting criteria for obesity (70%, χ^2=2.9, P=0.09). The presence or absence of psychiatric co morbidity for bipolar disorder, anxiety disorder or MDD did not differentiate remission rates nor did family history of psychiatric illness in general.

Clinical Response of PHQ-9 Scores

PHQ-9 scores decreased significantly with rTMS therapy for all groups and at an approximately equal rate for male and female patients. Repeated measures MANOVA of PHQ-9 scores for remitted and non-remitted patients controlling for gender (Figure 1) showed a significant main effect of time over the 6-week treatment period. An interaction effect identified proportionally larger reductions in PHQ-9 scores for the remitted patient group after 4 weeks of treatment which was lost after 5 weeks. Repeated measures MANOVA of PHQ-9 controlling for rTMS instrument (Figure 2) showed a significant interaction effect of time after 4 weeks of treatment and a significant Time X Remission Status X rTMS Instrument interaction effect suggesting a differential PHQ-9 response based upon rTMS unit selected for treatment. Except for the main effect of time, these secondary effects were lost at week 5.

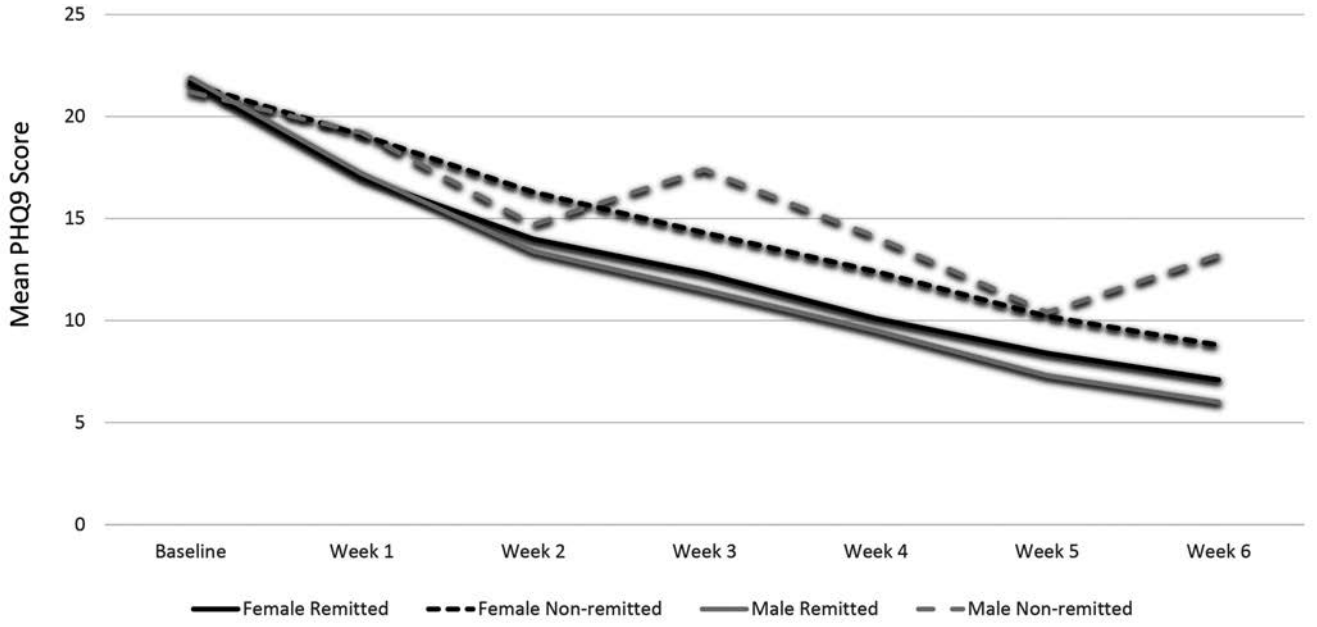
Effects of rTMS Instrument

A significant difference in clinical response rate was observed between

Table 1. Baseline subject characteristics.

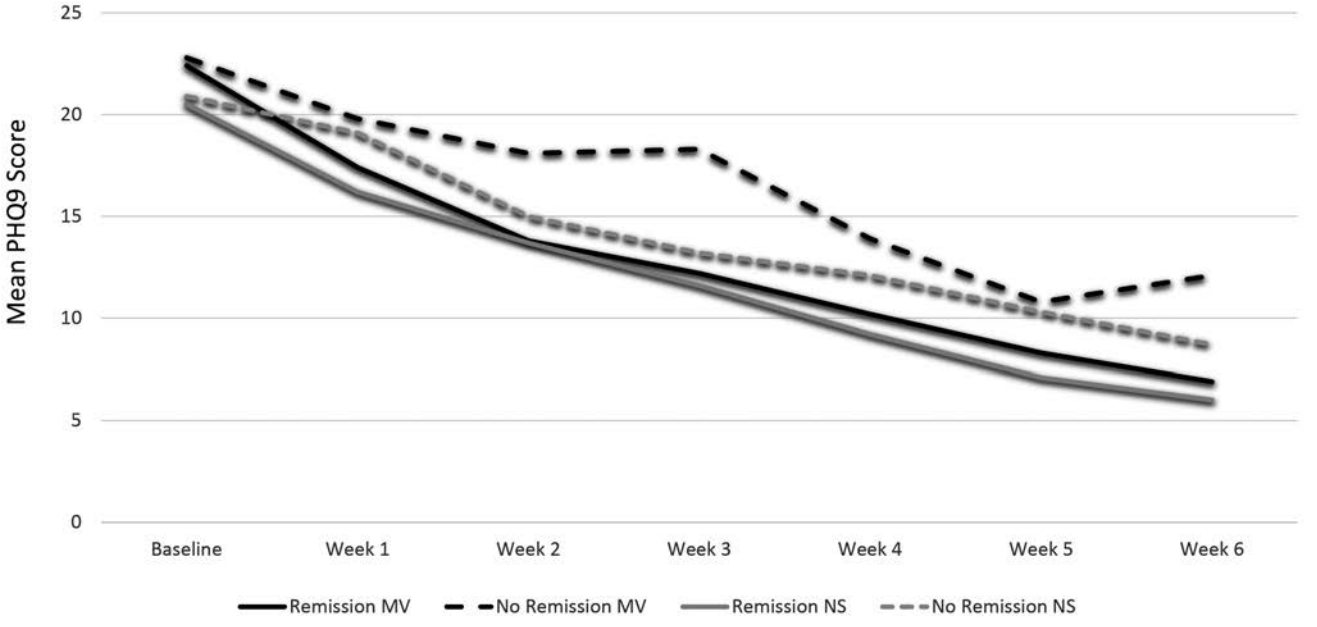
Variable	Male (N=98), N or Mean	Female (N=149), N or Mean	F/χ^2	P-value
Age	44.1±14 years Range 19-75 yrs.	42.1±13 years Range 18-78 yrs.	F=1.3	0.26
Baseline PHQ9 Score	21.7±4 Range 11-30	21.7±4 Range 3-27	F=0.02	0.90
Prior Inpatient Psychiatric Hospitalization	59 (60%)	95 (64%)	0.31	0.57
Previous Suicide Attempt	32 (33%)	58 (39%)	1.0	0.31
Substance Use History	21 (21%)	9 (6%)	13.1	0.0003
Smoking History	6 (6%)	7 (5%)	0.25	0.62
Sleep Problems	75 (76%)	119 (80%)	0.39	0.53
Intensive outpatient therapy	47 (56%)	88 (68%)	3.0	*0.08*
TMS unit "M" *vs* "N"	63 (66%)	80 (54%)	3.4	*0.07*

Baseline demographic characteristics by patient gender with bivariate analyses using Chi Squared test and General Linear Model. P<0.05 indicates a statistically significant difference for males versus females (bold). Statistical trends (P<0.1) are highlighted in italics.



Repeated measures MANOVA of PHQ-9 scores after 4 weeks on N=130 subjects showed a significant main effect of time (F=42.9, Num Df=4, Den Df=126, p<0.0001); a significant time*Remission effect (F=4.4, p<0.002); a trend for time*gender*remission status effect (F=2.2, p<0.07) and a between subjects effect of remission status (F=9.7, p<0.002). The interaction effects were lost at week 5. Solid lines represent PHQ-9 scores for remitted patients, dotted lines represent PHQ-9 scores for non-remitted patients. Black lines represent female patients and gray lines represent male patients.

Figure 1. PHQ-9 scores for male and female patients with remitted and non-remitted major depressive disorder after repetitive transcranial magnetic stimulation (rTMS).



Repeated measures MANOVA of PHQ-9 scores for N=130 patients after 4 weeks of rTMS showed a significant main effect of time (F=56.2, Num Df=4, Den Df=123, p<0.0001); a significant time*Remission effect (F=2.9, p<0.03); a significant time*TMS Unit*remission status effect (F=2.5, p<0.04) and a between subjects effect of remission status (F=10.9, p<0.001). Except for the effect of time, the interaction effects were lost at week 5. MV=Mag Venture and NS=NeuroStar rTMS units. Solid lines represent PHQ-9 scores for remitted patients, dotted lines represent PHQ-9 scores for non-remitted patients. Black lines represent patients treated using the MagVenture rTMS unit and gray lines represent patients treated using the NeuroStar rTMS unit.

Figure 2. PHQ-9 scores of patients with remitted and non-remitted major depressive disorder after repetitive transcranial magnetic stimulation (rTMS) using MagVenture or NeuroStar Units.

patients treated with the MagVenture (N=112, 78%) and NeuroStar (N=62, 63%) rTMS instruments (χ^2=7.1, P<0.008, Table 3). Baseline PHQ-9 scores for patients treated using the MagVenture (22.4±3.6; N=142) instrument were significantly higher than for the NeuroStar (20.7±4.6; N=98; F=11.3; P<0.001) indicating greater baseline severity. Bivariate analysis of the effects of rTMS unit was controlled using Cochran-Mantel-Haenszel test to assess the strength of association. The overall relationship between rTMS unit and clinical remission remained significant after controlling for the effects of gender (Cochran-Mantel-Haenszel test χ2=6.1; P<0.01), previous inpatient hospitalization (Cochran-Mantel-Haenszel test χ2=5.7; P<0.02), previous suicide attempt (Cochran-Mantel-Haenszel test χ2=4.6; P<0.03) and concurrent CBT (Cochran-Mantel-Haenszel test χ2=6.9; P<0.008). These results support a primary difference in response rate attributed to the rTMS instrument utilized showing increased remission rates for the MagVenture instrument.

Cochran-Mantel-Haenszel with Breslow Day test of common odds ratio was used to control for the effects of rTMS instrument on clinical response. A significant Breslow-Day test of common odds ratio (χ^2=4.9, P<0.03) supported a difference in the odds of clinical response to CBT based upon the rTMS unit utilized for treatment. The odds of clinical response to CBT were significantly greater when combined with rTMS using the MagVenture (Odds Ratio=3.2; 95% CI=1.2, 8.3) instrument whereas CBT had no effect on clinical remission rates using the NeuroStar instrument (Odds Ratio=0.72; 95% CI=0.29, 1.8). Similarly, patients with a previous history of suicide attempts had significantly greater odds of achieving remission when treated using the MagVenture (Odds Ratio=2.8, 95% CI=1.2, 6.7) instrument than if treated using the NeuroStar (Odds Ratio = 0.75, 95% CI=0.28, 2.0) as reflected by a significant Breslow-Day test of common odds ratio (χ^2=4.1, P<0.04). Further analyses considering the presence or absence of psychiatric co morbidity for bipolar disorder, anxiety disorder or major depressive disorder did not differentiate clinical response even after the effects of rTMS unit were controlled. Similarly, family history of psychiatric illness did not differentiate clinical response when the effects of rTMS unit were controlled.

Stepwise Logistic Regression

Stepwise logistic regression modeling was applied to identify the most parsimonious model to predict clinical remission of depression symptoms in response to rTMS therapy. The initial model parameters were based upon the findings from our examination and included: MagVenture rTMS instrument relative to NeuroStar, age, female versus male sex, presence of substance use history, previous suicide attempts, previous inpatient psychiatric hospitalization and concurrent CBT. The criteria for model entry was defined as P=0.25 and the criteria to stay were set at P=0.1. The global model converged and was significant (likelihood ratio test χ^2=16.3, df=3, P=0.001; Table 4). The final

Table 2. Clinical Remission Rates.

Variable	Rates		χ^2	P-value
	Male (N=98)	Female (N=149)		
Remission Rate	75(76%)	102(68%)	1.9	*0.17*
Clinical Remission Week	3.1±1 weeks Range 1-5 weeks	3.1±0.95 weeks Range 1-5 weeks	F=0.0	0.98
	Remitted	**Non-remitted**		
Age	42.5±14.1 years 18 to 75 years	43.8±13.4 years Range 20-78 years	F=0.45	0.50
Baseline PHQ9 Score	21.8±4 Range 8 to 30	21.5±4 Range 3 to 27	F= 0.32	0.57
Week 6 PHQ-9 Score	7.9±5.1 Range 0-25	10.3±6.3 Range 0-23	F=5.06	0.03*
	Trait Positive	**Trait Negative**		
Prior inpatient psychiatric hospitalization	120 (78%)	57 (61%)	7.9	0.005*
Previous Suicide Attempt	72 (80%)	105 (67%)	4.8	0.03*
Substance Use History	27 (90%)	150 (69%)	5.6	0.02*
Smoking History	9 (69%)	166 (71%)	0.03	0.86
Obesity (BMI≥30)	20 (87%)	157 (70%)	2.9	*0.09*
Sleep Problems	136 (70%)	41 (77%)	1.1	0.30
Intensive outpatient therapy	98 (72%)	53 (67%)	0.73	0.39

Clinical remission from depression symptoms was determined by clinician rating. Remission rates are presented for male versus female patients. Frequency of remission is presented for trait positive versus trait negative patients. P<0.05 indicates a statistically significant difference in remission rate (*). Statistical trends (P<0.1) are highlighted in italics.

Table 3. Remission Rates for TMS Units.

TMS unit (5 missing) Overall	Remitted (N=179) N (row %)	Not Remitted (N=70) N (row %)	χ^2	P-value
Mag Venture (N=145)	112 (78)	31 (22)		
NeuroStar (N=104)	62 (63)	37 (37)	7.1	**0.008**

Bivariate analysis of the relationship between rTMS instrument and rates of remission from depression symptoms. P<0.05 indicates a statistically significant difference in remission rate (bold). N=5 missing values.

model included MagVenture rTMS instrument (odds ratio=2; 95% CI= 1.1, 3.8), substance abuse history (odds ratio=3.3; 95% CI= 0.92, 11.6) and prior inpatient psychiatric hospitalization (odds ratio=2.1; 95% CI=1.1, 3.9) as the best fit model of clinician rated response to rTMS therapy. The Hosmer and Lemeshow Goodness-of-Fit test showed no lack of fit (χ^2=5.9; P=0.2).

Discussion

Our investigation of the effectiveness of rTMS and rTMS with CBT in the treatment of MDD and other related psychiatric comorbidities and conditions further supported the efficacy of rTMS in an applied clinical setting (AwakeningsKC, CNI). This was demonstrated by a clinical response rate >70% as assessed by clinician defined remission rates and a significant reduction of PHQ-9 scores over a 6-week treatment protocol. The effect of rTMS in our applied clinical setting was independent of family history risk factors and most psychiatric comorbidity lending support for the efficacy of selective targeting of the intervention on relevant neural circuitry, the specificity and independence of the clinical response to rTMS for MDD. The most important predictors of clinical response pertained to severity of depressive disorder as indicated by prior hospitalization, suicide attempts and co-morbid substance abuse which are important validating evidence of efficacy in the populations most in need. Comorbid substance abuse diagnoses, which occurred more frequently among males, showed higher remission when compared to patients who did not have a history of comorbid substance abuse. Full remission was also reached for all nine females comorbidly diagnosed with substance abuse and MDD.

There is an expected and slight variation in the position and MT excitability between individual rTMS patients with reduced cortical plasticity and interhemispheric communication reported among the elderly.[26,34,35] We found age to be correlated with the week clinical remission was achieved – with older age associated with longer time to remission. This is consistent with previous reports of reduced rTMS response in older men.[26] These results suggest reduced efficacy may be associated with age-related factors possibly through decreased neural plasticity, adaptability or remodeling capabilities. However, age did not appear to impact overall response rates after 6 weeks supporting a comparable benefit at all ages.

Our investigation also identified several unexpected factors that appeared to moderate clinical response of note and potential importance in future application of this technology in the clinical setting. AwakeningsKC- NCI has unique access and clinical experience utilizing two different rTMS instruments from different manufacturers with data available for consideration of relative efficacy. High clinical remission rates were found for both instruments which were reflected by significant reductions in PHQ-9 scores over the course of treatment. However, our analyses identified a potentially confounding effect attributable to the rTMS instrument utilized for treatment indicating a higher overall efficacy for the MagVenture over the NeuroStar instrument. These results remained significant after controlling for age, sex, severity and comorbidity indicators with clinical remission rates using the MagVenture instrument consistently superior to the NeuroStar. These differential effects of rTMS instrument moderated responsiveness to CBT which was significantly more effective when paired with rTMS using the MagVenture rather than using NeuroStar. Patients with a previous history of suicide attempts also had greater odds of achieving remission when treated using the MagVenture than NeuroStar.

Oliveira-Maia AJ *et al.*[36] used a retrospective design to compare clinical response rates for Neurostar (N=41) vs another rTMS instrument by Magstim (N=113, Eden Prairie, MN) in 154 patients treated up to 6 weeks with 20 Hz stimulation. Treatment response rates ranged from 44-57% for both rTMS instruments but did not significantly differ. The Magstim instrument also utilized a figure eight coil with similar capability to generate electrical fields over the brain surface. Patients treated on the NeuroStar instrument did not differ from the Magstim instrument in baseline characteristics or posttreatment depression severity as assessed by Beck Depression Inventory or Hamilton Depression Rating Scales. Our study had almost twice as many subjects treated using the NeuroStar instrument increasing statistical power to identify differences. Our patients treated using the MagVenture instrument also possessed significantly higher baseline PHQ-9 scores which may reflect non-random distribution based upon severity of illness. However, the differences remained significant even after the effects of gender, prior inpatient hospitalization, suicide attempts and CBT were controlled. Stepwise logistic regression modeling further supported clinical response using the MagVenture over the NeuroStar instrument for high severity cases with comorbid substance use disorder.

As described, the various rTMS instruments do possess qualitative differences in coil design, pulse width leading to perceptible differences including pain more commonly reported for the NeuroStar instrument. Further, the absence of a cooling mechanism on the NeuroStar instrument limits performance parameters requiring down-time to avoid overheating. Although validated for clinical use, it is not yet known whether repeated high-volume application of either TMS instrument in a daily practice setting, over time, could result in fluctuation of signal and differences in performance.

Study Limitations

The patients treated using the MagVenture instrument possessed significantly higher baseline PHQ-9 scores which may reflect a difference in treatment recruiting. The NeuroStar instrument was the first rTMS unit purchased at AwakeningsKC-CNI and it was utilized for treatment of MDD for two years before the MagVenture was purchased and utilized. The familiarity, knowledge, and experience with the techniques and instrumentation increased over time and practice leading to the admission of more mentally ill patients in treatment as time progressed which may have contributed to the differences observed in this

Table 4. Stepwise Logistic Regression Final Model.

Model Effects	Point Estimate (Odds Ratio)	95% Wald Confidence Limits	P-value
MagVenture vs NeuroStar rTMS Unit	2.0	1.1; 3.8	
Substance Abuse History	3.3	0.92; 11.6	
Inpatient Hospitalization	2.1	1.1; 3.9	
Likelihood Ratio Test of Global Null Hypothesis: Beta=0		χ^2=16.3; df=3	0.001
Hosmer and Lemeshow Goodness-of-Fit Test		χ^2=5.9; df=4	0.21

Stepwise logistic regression final model of clinical remission from depression symptoms after 6 weeks of treatment using rTMS. The model includes three co-variates with related odds ratios and 95% confidence intervals. The global model was signficant and the Hosmer-Lemeshow goodness-of-fit testing showed no significant lack of fit.

study. There was some attrition of participants due to a lack of funding from third party payers mainly impacting, patients >18 years of age, and those treated off label which reduced the sample size eligible for observation. There were no patients reported whom dropped out of treatment due to the treatment itself. Thirdly, due to the study being held in a clinical practice with no occurrences of recruiting outside of the office, this narrowed the population, as most of the patients were Caucasian (97%) and more than half were female (60%). There was only one year of follow up data taken following each individual's rTMS treatment due to external reasons such as patients moving, patients not scheduling appointments further, a lack of third-party payment, etc., which limited the scope of our analyses and findings. Otherwise, more than half of the patients included in this study followed-up consistently with the clinic, whether this be for medication management, CBT etc., and the results are encouraging.

Conclusions

Our investigation of the effectiveness of rTMS and rTMS combined with CBT in the treatment of MDD supported the efficacy of rTMS in an applied clinical setting. The results were consistent with previous reports and independent of comorbid psychopathology and family history. Our findings suggest that treatment outcomes may vary based upon the TMS instrument utilized (MagVenture vs NeuroStar) and further identified subgroups that may be more responsive to the MagVenture instrument than NeuroStar. These findings add to the body of literature and raise additional questions for future study.

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