

Repetitive Transcranial Magnetic Stimulation (rTMS) in Treatment Resistant Depression: Retrospective Data Analysis from Clinical Practice

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Abstract

Objective: The aim of this paper is to present the service data results from a clinical repetitive Transcranial Magnetic Stimulation (rTMS) service treating treatment resistant depression (TRD). **Methods:** The study was a retrospective investigation of routinely collected data on patients receiving rTMS between 2015 and 2018. Measures used were the clinician-rated Clinical Global Impression (CGI) and Hamilton Depression Rating Scale (HAM-D), and patient rated Physical Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder 7 (GAD-7). The outcome data of 144 patients with TRD was analysed. The sample included patients with co-morbid psychiatric diagnosis. **Results:** Response and remission rates respectively were 34.6% and 20.6% for the HAM-D; 10% and 28.6% for the PHQ-9; 31% and 31.8% for the CGI; and 24.6% and 28.8% for GAD-7. Effect sizes were mostly medium (0.48, 0.27, 0.51, 0.43 respectively). GAD-7 reliable change improvement was 56.1% and PHQ-9 reliable change improvement was 40%. There was a medium positive correlation between anxiety (GAD-7) and depression recovery (HAM-D), $r = 0.31$, $n = 46$, $p = 0.039$, with lower pre-treatment anxiety associated with lower post-treatment HAM-D scores. **Conclusions:** TRD patients with low pre-treatment anxiety levels respond to treatment better than those with high pre-treatment anxiety. The results show that a clinical rTMS service can have a significant impact on symptoms of depression and anxiety in TRD. The findings support wider availability of rTMS as a treatment option for people with TRD.

Keywords

Repetitive Transcranial Magnetic Stimulation (rTMS),

1. Introduction

The leading cause of disability worldwide is major depressive disorder (clinical depression); it is a major contributor to the overall global burden of disease (WHO, 2017). Depression can result in emotional, psychological and functional problems that can be detrimental to the well-being and health of those affected (WHO, 2017). The impact and treatment of depression carries a large cost to society through care and treatment costs and the loss of productivity and societal contribution of those affected (Greenberg et al., 2015). Relapse rates remain significant, highlighting the chronicity of depressive disorders for some (Huynh & McIntyre, 2008).

There is a lack of an accepted single definition of treatment resistant depression (TRD) (Berlim & Turecki, 2007). A US study reported that over 50% of people did not experience remission after first-line antidepressant treatment, and one-third did not experience remission after four courses of different treatment (Rush et al., 2006). A multi-site study in Europe reported that 50% did not respond to two consecutive courses of antidepressant treatment (Souery et al., 2007). The non-response rate to psychotherapy, most commonly cognitive behavioural therapy (CBT), has been reported as being 62% - 70% (Gyani et al., 2013; Griffiths & Griffiths, 2015). Therefore, many people do not respond to recommended treatments that are generally available in first world economies, and some who respond initially may relapse and become unresponsive to subsequent treatment.

Transcranial magnetic stimulation (rTMS) is a form of neuromodulation: a non-invasive and non-convulsive technique where a purpose-made electromagnetic coil is placed against the patient's scalp to deliver a short, powerful magnetic field pulse to induce electric currents in the cerebral cortex (Hardy et al., 2016). rTMS treatment usually comprises single daily sessions lasting about 30 minutes, over a period which is typically for 4 to 6 weeks (Hardy et al., 2016). Evidence suggests that rTMS results in changes in brain activity, metabolism and connectivity that relate to emotional processing (Kito et al., 2008). However, with many forms of antidepressant treatment, the exact mechanism of treatment action is unknown (Hardy et al., 2016).

In the United States the Food and Drug Administration (FDA) approved TMS for treatment of depression in 2008 (Janicak & Dokucu, 2015). In the UK, the National Institute for Health and Care Excellence (NICE) (NICE, 2015) declared it to be safe and effective in reducing depressive symptoms compared to sham TMS, and that treatment does not require either hospital admission or anaesthesia (NICE, 2015). Treatment can be carried out on an outpatient basis and rTMS was recommended for the treatment of depression, including TRD. NICE (NICE, 2015) noted that reports from patients were positive, and patients described sig-

nificant benefits to their quality of life, including some who felt able to withdraw from taking oral antidepressant medications (NICE, 2015).

A systematic review of 45 RCTs found rTMS to be robustly effective versus sham TMS on depression symptoms, response or remission; and that patients undergoing rTMS are twice as likely to achieve clinical response or remission compared to a sham procedure (Health Quality Ontario, 2016). Placebo response may be a component of therapeutic response to rTMS, and placebo response increase over time could indicate need for improvement in rTMS trial designs, including better sham versions of rTMS (Razza et al., 2018).

In research trials, response and remission rates have ranged between 25% - 50% and 12% - 35% respectively (Allan, Herrmann & Ebmeier, 2011; Berlim et al., 2014; Gross et al., 2007; Herrmann & Ebmeier, 2006; Kozel & George, 2002; Lam et al., 2008; Schutter, 2010; Slotema et al., 2010; Xie, Chen, & Wei, 2013). Following initial FDA clearance in 2008, a number of peer review published studies have reported remission and therapeutic response in clinical service settings which have ranged between 29% - 51% and 6% - 37% respectively (Carpenter et al., 2012; Connolly et al., 2012; Galletly et al., 2015; Taylor et al., 2017).

There is considerable research evidence for the effectiveness of rTMS in the treatment of depression from research trials. It is important to understand results in clinical practice. This study reports the patient characteristics and outcomes data from a service delivering rTMS within the United Kingdom's National Health Service (NHS).

2. Methods

2.1. Design

The study was a retrospective investigation of routinely collected data on patients receiving rTMS services between 2015 and 2018 at a UK based service provider. Inclusion criteria were adults (18 and over with diagnosis of TRD. Exclusion criteria: have an intracranial implant (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head (excluding the mouth), that cannot be safely removed.

Demographic information (gender, age at admission), diagnosis, treatment funder, and outcomes data were extracted from clinical records containing routinely collected data. Analysis was conducted using an anonymised database or routinely collected data and so ethical approval was not required.

2.2. Measures

The Hamilton Depression Rating Scale (HAM-D) is one of the most commonly used and extensively studied measures of depressive symptoms (Hamilton, 1960). Internal, inter-rater and retest reliability estimates are adequate for the global score (Hamilton, 1960; Bagby et al., 2004). The 2 item version was used, first 17 items scored. The Beck Depression Inventory (BDI) is one of the most widely used measures of depression severity (Beck & Alford, 2009). The scale has high content validity, construct validity, concurrent validities, content validity

internal consistency, and reliability (Jackson-Koku, 2016). The Clinical Global Impression score (CGI) rating scale is one of the most widely used assessment instruments in psychiatry (Guy, 1976). The Clinical Global Impression Scale (CGI) is a brief clinician-rated instrument of illness severity. There is a lack of strong evidence for the validity and therefore it is recommended as part package of assessments (Forkmann et al., 2011). The PHQ-9 is a self-report measure of depression; it has good sensitivity and a specificity for major depression and good internal consistency (Kroenke et al., 2001). The GAD-7 originates from Spitzer et al. (2006) and is a self-report measure of generalised anxiety disorder; it has good sensitivity and specificity for generalised anxiety disorder and good internal consistency (Kroenke et al., 2007). Higher scores on all scales indicate greater severity. The measures were collected prior to treatment and shortly following final first course of treatment.

2.3. Process to Treatment

Patients with depressive symptoms are referred to the service by their GP or psychiatrist. A medical and physical history is taken and patients are then assessed for a diagnosis of TRD by a psychiatrist working in the neuromodulation unit. TRD is defined as non-response to 2 or more appropriate courses of anti-depressants. rTMS protocol and length of treatment are set by the psychiatrist. Patients who lack capacity to consent to treatment are excluded. Patients are provided with information about the treatment (procedures, risks, side effects, remission/response rates) and are required to sign a “consent to treatment” form before treatment commences; they can withdraw consent at any point. rTMS equipment suppliers are Magstim and MagVenture.

2.4. rTMS Treatment

The site of stimulation is determined using EEG cap and treatment at F3 (Tsuzuki et al., 2016). The majority of patients (n = 68, 93.2%) received of FDA (Food and Drug Administration, 2011) depression protocol high frequency stimulation to left dorsolateral prefrontal cortex. Five (6.8%) received Hadley et al. (2011) depression protocol high frequency stimulation to left dorsolateral prefrontal cortex. Of these, 18 (24.7%) patients with depression and generalised anxiety (as measured with the GAD-7 (Spitzer et al., 2006) additionally received right DLPFC inhibitory rTMS (Dilkov et al., 2017), immediately prior to delivery of FDA left dorsolateral prefrontal cortex depression treatment. This additional treatment option was added to the service in October 2016. The average strength of magnetic field was 63.84% (SD = 6.224, range: 43 - 75). During this period there were no seizures and two syncopal episodes.

2.5. Analysis

Analysis of change from baseline to post first course treatment scores was carried out using data from 144 patients. Not all patients had data sets for all measures and so numbers per measure vary. For categorical responses, we defined

responses as a 50% or greater drop on the last assessment of treatment, and 25% - 49% drop as a partial response. Remission was defined as CGI-S score as ≤ 2 , PHQ-9 ≤ 9 , GAD-7 ≤ 7 and HAM-D ≤ 7 (Gyani et al., 2013).

As continuous variables were not normally distributed, Wilcoxon signed-rank tests (Z) were used to compare baseline with post-treatment measures, together with the calculated effect sizes. Using non-parametric analysis (Pearson chi square test and Mann-Whitney U test), the differences in demographic variables and between responders and non-responders on a number of variables were explored. All tests were 2-sided, at 1% level of statistical significance. Spearman's rho was used to calculate correlations. Data were analysed using statistics software package SPSS.

3. Results

3.1. Patient Characteristics

The data was collected on a sample of 144 patients with TRD, who were treated between January 2015 and October 2018, see **Table 1**. Cross tabulation indication that female patients were overrepresented, χ^2 (df = 1, $n = 144$) = 5.44, $p = .020$. There were no difference in HAMD between genders ($n = 91$, $U = 993.0$, $p = .509$) and age ($n = 91$, $U = 1059.0$, $p = .718$). Similarly, age and gender had no effect on CGI and BDI scores.

Co-morbid diagnosis was as follows: generalized anxiety disorder (GAD) ($n = 76$, 52.8%); bipolar affective disorder ($n = 13$, 9%); chronic fatigue syndrome ($n = 5$, 3.5%); psychosis, emotionally unstable personality disorder, autism spectrum disorder (ASD), bulimia nervosa ($n = 4$, 5.5%); post-traumatic stress disorder (PTSD), cocaine dependence, obsessive-and compulsive disorder ($n = 3$,

Table 1. Demographic and Clinical Characteristics of the rTMS sample ($n = 144$).

Characteristic	
Age, Mean \pm SD (Min-Max)	48.96 \pm 15.10 (19 - 80)
Sex, n (%)	
Male	40.3%
Female	59.7%
Treatment, n (%)	
NHS	77.1%
Private	22.9%
TX, n, Mean \pm SD (Min-Max)	
Depression	123, 25.15 \pm 7.05 (10 - 43)
Anxiety	58, 15.91 \pm 8.64 (1 - 37)
Depression Protocol, n (%)	
Standard FDA	121 (84.1%)
Hadley 6000	6 (4.9%)
Theta Burst Stimulation	2 (1.4%)

2.1%); alcohol dependence, and intentional self-harm ($n = 2$, 1.4%); chronic pain syndrome, anorexia, schizoaffective disorder, dysthymia, fibromyalgia, mixed and other personality disorder, narcissistic personality disorder, Parkinson's disease, social phobia generalised, and paranoid delusional disorder ($n = 1$, 0.7%).

3.2. rTMS Treatment Outcome

Baseline depression and anxiety scores were in the moderate to severe range (see **Table 2**). There was a statistically significant improvement on all measures after the rTMS treatment, with small to medium effect sizes.

3.3. Clinician Assessed (HAMD) and Self-Reported Measures (CGI/PHQ-9) of Depression

Beginning with pre-treatment measures, there was a weak, positive correlation between HAMD and CGI, $r = 0.29$, $n = 82$, $p = 0.008$, and a strong positive correlation between HAMD and PHQ-9, $r = 0.59$, $n = 40$, $p < 0.001$. With post-treatment measures, there was a strong, positive correlation between HAMD and CGI, $r = 0.85$, $n = 61$, $p < 0.001$, and a strong positive correlation between HAMD and PHQ-9, $r = 0.74$, $n = 23$, $p < 0.001$. This level of correlation would suggest that both self-reported and clinician assessed measures are likely measuring the same construct.

3.4. GAD Defined Anxiety Rates in TRD patients

There was a statistically significant positive correlation ($p < 0.05$) between all four post-treatment measures (Spearman's rho ranging from 0.695 between HAMD and GAD-7, to 0.846 between HAMD and CGI). Pre-treatment correlations were similar.

Table 2. Mean (SD) pre- and post-treatment scores, mean change in scores and associated Wilcoxon Signed Ranks significance tests for patients treated with rTMS.

Rating scale	<i>N</i>	Mean \pm SD [range]	<i>Z</i>	<i>p</i>	<i>r</i>
HAM-D					
Pre	119	21.27 \pm 5.90 [6 - 38]	-6.95	<0.001*	0.48
Post	91	11.86 \pm 6.60 [0 - 27]			
CGI					
Pre	88	4.98 \pm .88 [3 - 7]	-6.34	<0.001*	0.51
Post	65	2.65 \pm 1.19[1 - 6]			
GAD7					
Pre	89	14.34 \pm 4.72 [2 - 23]	-5.38	<0.001*	0.43
Post	70	10.23 \pm 6.17 [0 - 21]			
PHQ9					
Pre	53	17.98 \pm 6.23 [2 - 29]	-2.50	0.012*	0.27
Post	35	13.11 \pm 7.75 [0 - 27]			

*Statistically significant $p < 0.05$.

Anxiety and depression have been demonstrated to be highly comorbid (Kaufman & Charney, 2000), so the relationship between GAD-7 scores and measures of depression (HAMD/CGI/PHQ-9) was investigated using Spearman rank order correlation coefficient. Beginning with measures taken pre-treatment, there was a medium, positive correlation between GAD-7 and HAMD, $r = 0.42$, $n = 71$, $p < 0.001$, a medium positive correlation between GAD-7 and PHQ-9, $r = 0.30$, $n = 50$, $p = 0.035$, and no significant correlation between GAD-7 and CGI, $r = 0.03$, $n = 47$, $p = 0.821$. With post-treatment measures, there were strong, positive correlations between GAD-7 and HAMD, $r = 0.70$, $n = 46$, $p < 0.001$, GAD-7 and CGI, $r = 0.74$, $n = 26$, $p < 0.001$, and GAD-7 and PHQ-9, $r = 0.74$, $n = 34$, $p < 0.001$

Spearman's Rho was further used to investigate the relationship between level of anxiety (GAD-7) pre-treatment and depression (HAM-D) recovery. There was a medium positive correlation between the two variables, $r = 0.31$, $n = 46$, $p = 0.039$, with lower pre-treatment anxiety associated with lower post-treatment HAM-D scores.

Using binary logistic regression, no primary outcomes (age, gender, number of treatment sessions for depression and anxiety) were found to be statistically significant predictors of remission rates for HAMD, CGI, GAD-7 and PHQ-9.

3.5. Categorical Response and Remission Rates

The highest response rate was elicited by the HAMD, followed by the CGI, GAD-7 and the PHQ-9 (see Table 3), whereas the highest remission rate was elicited by CGI, followed by the GAD-7, PHQ-9 and the HAMD.

3.6. Reliable Change Index

Reliable change analysis was undertaken based on the work of Jacobson and Traux (1991). Cronbach's α values of 0.89 (Kroenke et al., 2001) and 0.92 (Kroenke et al., 2007) were used for PHQ-9 and GAD-7 respectively. Reliable change was calculated to be 3.7 for GAD-7, and 5.72 for PHQ-9. As changes in individual patients scores must take integer value, this means that a patient must have shown a pre-treatment to post-treatment change of at least 4 points for GAD-7 and 6 points for PHQ-9 to be considered reliable. Reliable improvement results are presented in Table 4.

Table 3. Response partial response and remission rates (%).

	Response	Partial Response	No Response	Remission
HAMD	34.57%	37.04%	28.39%	20.59%
CGI	31.03%	46.55%	22.41%	31.76%
GAD-7	24.56%	35.09%	40.35%	28.75%
PHQ-9	10%	33.33%	56.67%	28.57%

Table 4. Reliable improvement and deterioration.

Measure	Improvement (%)	Deterioration (%)
GAD-7 (Reliable change set at 4)	56.1%	5.3%
PHQ-9 (Reliable change set at 6)	40%	16.7%

4. Discussion

The results show that rTMS significantly improved all measures of depression and anxiety. Response and remission rates for depression were 34.6% and 20.6% for the HAM-D; 10% and 28.6% for the PHQ-9; 31% and 31.8% for the CGI; and for anxiety they were 24.6% and 28.8% (GAD-7). Effect sizes were medium, except for PHQ-9 which was low. Reliable change analysis of GAD-7 and PHQ-9 indicated greater improvement in self-reported anxiety than depression. The reliable change in anxiety was similar to that which has been achieved through a national programme of psychotherapy for moderate to severe anxiety (Richards & Borglin, 2011; Griffiths & Griffiths, 2015). The study's findings support published rTMS results showing a positive impact on depression and anxiety (Carpenter et al., 2012; Connolly et al., 2012; Galletly et al., 2015; Health Quality Ontario, 2016; Taylor et al., 2017).

There were no differences found in recovery rates between males and females, or age. While there has been previous research that showed younger patients responded better to rTMS (Pallanti et al., 2012), a number of studies have been unable to show any difference in rTMS response between both age and gender (Conca et al., 2000; Ciobanu et al., 2013; Rosenich et al., 2018).

Correlations between clinician and self-assessed measures of depression suggest that both types of measures are likely measuring the same construct. This supports previous research showing that both types of assessments can be used to significantly predict the outcome of the other (Uher et al., 2012). This strengthens the case for a multi-method approach enabling clinicians to build up a complete profile of their patients (Möller, 2000).

Our findings suggest that TRD patients with low pre-treatment anxiety levels were found to respond to antidepressant treatment better than those with high pre-treatment anxiety. This is in line with previous research on antidepressants showing non-responders score higher on anxiety measures, and those with anxious depression take longer to respond to treatment than those with non-anxious depression (Conca et al., 2000; Flint & Rifat, 1997).

5. Limitations

Data was extracted from a clinical database and patient notes with some missing assessments, evidenced by the different number of subjects available for analysis on each outcome measure. Treatment was open label and adjunct to any existing antidepressant treatments, with the absence of a control. Data was from a single site in the UK limiting generalizability, however; patients were from across the

UK, partially negating this.

6. Conclusion

This study ADDS to the findings of other published service data that outpatient delivered clinical rTMS is effective. Further work is needed to define the role of rTMS in a depression healthcare service pathway. This work needs to understand when it is best to offer rTMS in people's experience of depression and when rTMS is a better option than other treatment options such as switching antidepressants or ECT.

The availability of rTMS is currently limited. The results support wider availability of rTMS as a treatment option for people with TRD. Ideally, rTMS should be a treatment option which is freely available to people with TRD who meet the criteria for treatment rather than just those who can afford the costs of private treatment or who have insurance to cover costs.

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None.

Conflicts of Interest

Professor Alex O'Neill-Kerr is a consultant for Magstim. The other authors have no conflicts of interest, and the work was not supported or funded by a company.

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