

Repetitive transcranial magnetic stimulation for major depression and obsessive-compulsive disorders in Singapore

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ABSTRACT

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is used for treatment-resistant major depressive disorder (MDD) and obsessive-compulsive disorder (OCD), but there are few studies on patient outcomes in Southeast Asia. In this study, we describe the clinical profile and outcome of patients with MDD and OCD treated with rTMS in Singapore.

Method: A naturalistic retrospective study of 71 patients (inpatient and outpatient) who received rTMS treatment between June 2018 and April 2023 was conducted. The depressive and obsessive outcome rating scales used were clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Clinical Global Impressions-Severity (CGI-S) and self-rated Depression Anxiety and Stress Scale-21 (DASS-21).

Results: Clinician-rated and self-rated mood and general condition improved significantly. MADRS mean score improved from 28.1 (standard deviation [SD] 7.3) to 20.7 (SD 10.1) ($P<0.0001$) (20.8% response rate/17% remission rate). CGI-S mean 4.6 (SD 0.8) improved to 3.3 (SD 1.2) ($P<0.0001$). DASS-21 total mean improved from 67.3 (SD 24.6) to 49.6 (SD 28.0) ($P<0.0001$). Y-BOCS mean score displayed a trend towards improvement from 30.1 (SD 7.5) to 27.2 (SD 6.9) ($P=0.799$). However, 44.4% of patients with OCD responded with a minimal 20% reduction in baseline Y-BOCS. Moreover, the subgroup of 35.8% of patients with less than 30 rTMS sessions had contributed disproportionately to nonresponse (85.7%). Patients who received rTMS treatment (>30 sessions) had a trend of larger improvement of MADRS score when compared to patients with (≤ 30 sessions) (9.4 [SD 9.7] versus 3.8 [SD 12.3] [$P=0.078$]).

Conclusion: Response and remission rates for MDD and OCD suggest patients have a good response to rTMS treatment. Dosing longer rTMS sessions after an acute course helps to maximise effectiveness. Further research to determine predictors of outcome and characterise clinical features of late responders to target treatment more effectively is recommended.

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Keywords: major depressive disorder, naturalistic, obsessive-compulsive disorder, remission, repetitive transcranial magnetic stimulation, response

CLINICAL IMPACT

What is New

- This is one of the largest naturalistic study reporting outcomes of rTMS therapy in Southeast Asia for the treatment of major depression and obsessive-compulsive disorders.

Clinical Implications

- This study demonstrated that rTMS treatment was a rapid-acting, effective, safe and well-tolerated alternative treatment option for treatment-resistant depression and obsessive-compulsive disorders.
- This finding could affect the clinical practice of rTMS dosing. Dosing additional rTMS treatment with more than 30 sessions might help more patients with major depression to have a meaningful improvement.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a novel and noninvasive neuromodulation therapy used for treatment-resistant major depressive disorder (MDD)¹ and obsessive-compulsive disorder (OCD).² OCD and depression are disabling psychiatric disorders, which have a detrimental impact on individuals, their families and society.^{3,4} The lifetime prevalence of depression is high at 5.8% and OCD affects 1 in 28 Singaporeans.⁵ Depression contributes substantially to the global burden of disease and disability.⁶ However, despite effective pharmacological and psychological interventions, approximately 40% to 50% of patients have not responded satisfactorily to standard treatment.⁷

rTMS involves placing an electromagnetic coil against the scalp, which generates repetitive pulses to depolarise neurons in the outer cortex of the brain (via an alternating magnetic field).⁸ Following the US Food and Drug Administration clearance

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in 2008 for MDD¹ and in 2018 for OCD, rTMS has been adopted into routine clinical practice and established a favourable effectiveness and safety profile for psychiatric disorders. It has emerged as a mainstream treatment in many developed countries,^{9,10} including Singapore, where the College of Psychiatrists endorsed the use of rTMS for depression in 2015 and OCD in 2018.¹¹ rTMS service is provided by the Institute of Mental Health, Singapore's only tertiary psychiatric hospital, with 1900 inpatient beds and about 40,000 outpatients.¹²

Most recent naturalistic and registry studies of the rTMS treatment of MDD reported that overall response and remission rates have ranged between 29% to 51% and 6% to 37%,^{13–18} respectively. Although rTMS for treating OCD has been promising, Rostami et al. reported a response rate of 46.2%, based on a 30% reduction of Yale–Brown Obsessive Compulsive Scale (Y-BOCS) baseline scores.¹⁹ The efficacy of rTMS treatment for naturalistic OCD patients remains under-explored. rTMS is well accepted by both patients and psychiatrists due to its cost-effectiveness²⁰ and the absence of serious side effects.

The optimal dosage of rTMS is unknown. rTMS outcomes were heterogeneous based on response trajectory.^{21,22} Hence, there was no gold standard regarding rTMS dosing across clinics: Griffiths et al. averaging 26.6 sessions (standard deviation [SD] 9.45),¹⁵ Dowling et al. reported 20 sessions¹⁴ and Carpenter et al. reported an average of 28.1 sessions (SD 10.1)¹⁷ for MDD. Studies examining the number of rTMS sessions on the clinical outcome are inconclusive. In an Australian study, 40% of patients who were nonresponsive to the previous course responded to second and third courses with the same rTMS modalities.¹³ On the contrary, Dowling et al. underscored the possibility that briefer rTMS courses (20 courses over 4 weeks) contribute to a superior response rate of 54% and remission rate of 28%.¹⁴ Additionally, Feffer et al. found that with early treatment response achieved at 10 sessions,²² the effectiveness of rTMS might diminish or plateau despite continued treatment with more sessions of previous modalities. Therefore, consistent and robust dose-response effects had not yet emerged. Guidelines in Singapore suggested that rTMS requires at least 30 sessions for optimal therapeutic effects, with some individuals possibly benefiting from longer courses.¹¹ rTMS was often perceived to be inconvenient and costly. Patients' access to additional courses was limited due to cost and time commitment. The Ministry of Health (MOH), Singapore has approved a subsidy to cover the expense of rTMS treatment for an initial 24

sessions.²³ Patients had to self-pay for additional sessions in case of delayed response or not having achieved remission. Given the logistical burden of rTMS, there was a need to understand the average trajectory of symptom changes during the rTMS course, and the patient profile might benefit from the prolonged treatment course.

To date, studies describing rTMS service in Southeast Asia remain limited. Clinical trials in Singapore with a similar multiethnic Asian population demonstrated the efficacy of rTMS.^{24,25} However, participants were subject to restrictive selection criteria. In naturalistic studies, patients differ from those recruited in research and have a broader range of symptomatology and comorbidity.²⁶

This study addressed the gap with 2 main objectives. First, we aimed to describe the clinical profile and outcome of rTMS (response and remission rates). We sought to compare symptomatic changes in subgroups (MDD and OCD) from pre- to post-rTMS treatment. Second, we aimed to examine whether dosing additional treatment (>30 sessions) resulted in further meaningful clinical improvement for MDD. Hutton et al. suggested that rTMS courses with less than 30 sessions are associated with inferior endpoint outcomes.²⁷ We hypothesised that the cohort where patients received longer treatment courses had a trend of a larger reduction in depressive symptoms.

METHOD

Study participants

We retrospectively analysed a dataset of patients who received rTMS between June 2018 and April 2023 at the Institute of Mental Health, Singapore. Patients were included if they: (1) received rTMS for a primary diagnosis of MDD and OCD; (2) are ≥ 18 years old; (3) had completed both baseline and post-treatment assessment measures. Exclusion criteria included the following: (1) drug or alcohol abuse or dependence (preceding 3 months); (2) unable to give informed consent; (3) acute suicidality; (4) significant neurological disorder, which may pose an increased risk to rTMS (epilepsy); (5) metal in the cranium, metallic implants, skull defects, pacemaker or other implantable electronic devices; (6) pregnancy. Patient's sociodemographic and clinical characteristics, including rTMS treatment and outcome, were extracted from the Clinical Alliance and Research in Electroconvulsive Therapy and Related Therapies (CARE) research database.²⁸ Ethical approval to conduct the study was obtained from the National Healthcare Group's Domain Specific Review Board (Reference no.: 2023/00415).

Patients were referred for rTMS assessment by attending psychiatrists who had made clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition. The patients were typically referred for treatment-resistant MDD/OCD. The subgroup of patients treated for OCD with comorbid depressive symptoms was grouped under the “OCD” diagnosis.

rTMS procedure

Before receiving rTMS treatment, patients were assessed by a psychiatrist who confirmed the patient's suitability. The pre-rTMS assessment included thoroughly screening the patient's sociodemographic, medical and psychiatric history. The individualised treatment dose was determined via the resting motor threshold (RMT) from the respective first dorsal interosseous muscle for dorsolateral prefrontal cortex (DLPFC) targets or foot motor cortex for OCD and dorsomedial prefrontal cortex (DMPFC).¹ All patients gave written consent.

After the rTMS psychiatrist's assessment and determination of the treatment dosage, trained nurses conducted scalp measurement and pre-treatment screening for patients at the next visit. Patients experienced the feel of the stimulation on their hands before the actual treatment. During treatment, rTMS was conducted in a room with facilities to manage seizures. Patients were seated in a reclining chair with earplugs. The treatment dosage started low (80% of RMT), and intensity was slowly ramped up based on the patient's tolerability. On average, patients achieved the prescribed dosage by the 4th session. Nurses observed the patient and made minor adjustments if the coil is out of place. Nurses also ensured the patients are comfortable by asking how they are faring. Patients signalled to the nurse if they wish to request time out. Patients with OCD experience the treatment regimen differently, as nurses are required to provoke the patient using the provocation script. The tailored provocation scripts were prepared by psychologists and designed to activate patients' OCD traits and brain circuitry.

rTMS was delivered using TMS machine MagPro X100 and Coil Cool D-B80 (MagVenture Inc, GA, US). Scalp-based measurements of the distance between tragus to tragus, and nasion to theinion, accounting for head circumference and size, were used to ensure accurate coil placement. The scalp measurement procedure requires patients to wear treatment caps snugly. Nurses will verify the consistency of treatment cap placement prior to

each treatment. Patients were treated using 1 of the 5 protocols: (1) in the high frequency (HF)-rTMS protocol, 10 Hz, 3000 pulses with 120% of motor threshold were delivered to the left DLPFC. The Beam F3 method was used to locate the DLPFC, following the location coordinates using the Beam F3 software (X and Y+1.5 cm). (2) In the low frequency (LF)-rTMS protocol, 1 Hz, 1500 pulses with 120% RMT were delivered to the right DLPFC. (3) In the dorsomedial (DM)-rTMS protocol, 20 Hz, 1200 pulses with 120% motor threshold were delivered to DMPFC, defined as 25% of the distance between the nasion to theinion along the midline of the head. The coil handle alternates from the right and left sides of the head.²⁹ (4) In the AF8-rTMS protocol, 1 Hz, 720 pulses with 120% RMT were delivered to the right orbitofrontal cortex, defined as 10% of the distance between the nasion to theinion anterior to the vertex in the sagittal plane, then 10% of head circumference to the right. The coil was orientated laterally with a handle perpendicular to the axial plane of the head.³⁰ (5) In the OCD-rTMS protocol, 2000 pulses with 100% RMT were delivered over 4 cm anterior to the optimal spot on the scalp, stimulating bilateral feet. The type of treatment and number of rTMS sessions were prescribed by the rTMS psychiatrist. Generally, 1 standard treatment course lasts about 20–30 minutes for 5 daily sessions per week, up to 24–30 sessions over 4–6 weeks, followed by maintenance treatment. Subsidies approved by MOH are currently only available for treatment-resistant major depressive disorder for the first 24 sessions in an acute course. Patients must self-pay a small amount of cash out of pocket. The cost of extended rTMS sessions was paid entirely by the patients. All patients received a standard course of 30 daily treatments. Those who achieved a >25% Montgomery–Åsberg Depression Rating Scale (MADRS) improvement at session 30 were offered additional treatment to optimise treatment response and durability. Clinically, the rTMS psychiatrist stopped at 30 sessions based on whether patients showed ≤25% improvement in MADRS score. Factors to consider in extending the acute course include a history of late response to anti-depressant treatment in prior episodes, having a lengthy duration of present episodes, being highly treatment-resistant, ability to pay, tolerability and convenience.³¹

Outcome measures

The MADRS,³² Y-BOCS³³ and Clinical Global Impressions-Severity (CGI-S)³⁴ were assessed by the rTMS psychiatrist at baseline, and then fortnightly or after every 10 treatments until

completion of the acute course. Depression Anxiety and Stress Scale-21 (DASS-21)³⁵ was administered as a self-rated scale weekly.

MADRS was used to measure depression severity. The response was defined as a reduction $\geq 50\%$ from baseline in MADRS score, and remission was defined as an MADRS score ≤ 10 .³⁶ Y-BOCS were used to assess the clinical severity of obsessive symptoms, and the response rate is defined by a 20% or less reduction in baseline Y-BOCS score. The MADRS, Y-BOCS, CGI-S and DASS-21 were the primary outcome measures, and the other measures were treated as secondary measures.

Statistical analysis

A descriptive analysis was performed for sociodemographic, clinical rTMS characteristics and baseline assessment scores. Paired t-tests were used for continuous variables and chi-squared tests for categorical variables. Continuous variables were presented as mean (SD), whereas categorical variables were presented as percentages.

The number of rTMS treatment sessions was stratified into ≤ 30 sessions and > 30 sessions. The trend difference in changes of MADRS scores from baseline to post-treatment in the 2 subgroups was analysed by Levene's test for equality of variances and paired t-test. All statistical analyses were conducted using IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY, US). Statistical significance was set at $P < 0.05$.

RESULTS

Patient sociodemographic and clinical characteristics

A total of 71 patients (MDD 58 [81.7%]/OCD 13 [18.3%]) received a mean average of 47.8 (SD 40.5) rTMS sessions. The mean average age was 33.6 (SD 14.8), and there were more females (60%). Of the 71 patients, 33.8% were highly educated (defined by education level above university). The largest ethnic group was Chinese (73.2%), compared to Indian (14.1%), Malay (5.6%) and Others (7.0%).

This study population was mostly severely ill (based on baseline CGI-S score) and was typically referred for rTMS due to treatment resistance to pharmacological treatment (64.8%) with more than 24 months of illness duration (29.6%) and 3 or more previous episodes of their illness (28.2%). The majority of the rTMS treatment was left DLPFC (45%). Patients were receiving treatment with concomitant medications/therapy: antidepressants (73.2%), benzodiazepine (47%), clozapine (5.6%) and antipsychotics besides clozapine (40%);

and 21.2% had tried electroconvulsive therapy (ECT) in the past.

Safety and tolerability

To ensure tolerability during stimulation, patients will undergo periodic mood assessments by rTMS psychiatrists after every 10th treatment. In addition, before and after each rTMS session, patients will be asked about any side effects and adverse events experienced. Spontaneous reports of side effects will be documented, and the rTMS psychiatrist will be notified. Most patients treated with rTMS reported no significant adverse events. There have been no seizures or mood switches to mania. The commonly reported adverse side effects were localised discomfort and mild headaches during the first week of treatment.

rTMS treatment outcome

For patients diagnosed with depression, rTMS induced an improvement in depressive symptoms. The response rate and remission rate were 20.8% and 17%, respectively. The MADRS total mean score improved from a baseline of 28.1 (SD 7.3) to 20.7 (SD 10.1) ($P < 0.0001$). The patients were assessed as "markedly ill" based on CGI-S baseline mean score, which improved significantly ($P < 0.0001$), from 4.6 (SD 0.8) to 3.3 (SD 1.2). For self-rated scales, DASS-21 total mean score improved from 67.3 (SD 24.6) to 49.6 (SD 28.0) ($P < 0.0001$) (Table 2).

Y-BOCS displayed a trend towards improvement from 30.1 (SD 7.5) to 27.2 (SD 6.9) ($P = 0.799$). However, 44.4% of patients with OCD responded with at least 20% reduction in baseline Y-BOCS (Table 3).

Clinical outcome is stratified by the number of rTMS treatment sessions

We further examined clinical outcomes in MDD patients based on the number of rTMS sessions. The subgroup of 35.8% of patients with less than 30 rTMS sessions had contributed disproportionately to nonresponse (85.7%). Patients who received rTMS treatment (> 30 sessions) had a trend of larger improvement of MADRS score when compared to patients with (≤ 30 sessions) (9.4 [SD 9.7] vs 3.8 [SD 12.3] [$P = 0.078$]) (Tables 4 and 5).

DISCUSSION

To our knowledge, this is the largest naturalistic study reporting outcomes in rTMS therapy in Southeast Asia for the treatment of MDD and OCD. This study demonstrated that rTMS treatment was a rapid-acting, effective, safe and well-tolerated

Table 1. Sociodemographic and clinical characteristics of the study sample.

Patient characteristics		Mean	SD
Age	71 patients	33.6	14.8
Average no. of rTMS sessions	70	47.89	40.5
		N	Percentage
Sex	Female	43	60.6
	Male	28	39.4
Ethnicity	Chinese	52	73.2
	Indian	10	14.1
	Malay	4	5.6
	Others	5	7.0
Education level	University and above	24	33.8
	College/Junior college	19	26.7
	The Institute of Technical Education/Diploma	9	0.1
	Secondary and below	13	18.3
MDD treatment sessions ^a	≤30 sessions	19	35.8
	>30 sessions	34	64.2
OCD treatment sessions	≤30 sessions	5	38.5
	>30 sessions	8	61.5
Diagnosis	OCD	13	18.3
	MDD	58	81.7
Treatment sites	F3	32	45.1
	F4	13	18.3
	OCD spot	13	18.3
	DMPFC	2	2.8
	AF8	11	15.5
Switching of rTMS modality	No	48	67.6
	Yes	22	31.0
Admission status	Inpatient (involuntary)	11	15.5
	Inpatient (voluntary)	18	25.4
	Outpatient	41	57.7
Duration of current episode ^a	Acute (≤12 months)	19	26.8
	Sub-acute (13–24 months)	11	15.5
	Chronic (>24 months)	21	29.6

Table 1. Sociodemographic and clinical characteristics of the study sample. (Cont'd)

Patient characteristics		N	Percentage
Previous depressive episode, range ^a	0	5	7.0
	1–3	17	23.9
	>3	20	28.2
Main reasons refer to TMS treatment	Difficult to treat with medications (poor tolerability/risks)	2	2.8
	Failure of medications	46	64.8
	Suicide	4	5.6
	Patient preference	6	8.5
	Previous good response to this treatment modality	1	1.4
	Others	1	1.4
Antidepressant ^a	No	5	7.0
	Yes	52	73.2
Clozapine ^a	No	52	73.2
	Yes	4	5.6
Antipsychotics other than clozapine ^a	No	27	38.0
	Yes	29	40.8
Lithium ^a	No	46	64.8
	Yes	10	14.1
Anticonvulsant ^a	No	39	54.9
	Yes	18	25.4
Stimulant ^a	No	51	71.8
	Yes	6	8.5
Benzodiazapine ^a	No	23	32.4
	Yes	34	47.9
No. of failed antidepressants	Failed ≥3 antidepressant	47	66.2
	Failed 1–2 antidepressant	15	21.1
	Failed 0 antidepressant	1	1.4
Past use of/Response to ECT ^a	No prior ECT	40	56.3
	Good response to prior ECT	2	2.8
	Partial response to prior ECT	6	8.5
	Poor response to prior ECT	7	9.9

^a Data total not complete due to missing value

AF8: right orbitofrontal cortex; DMPFC: dorsomedial prefrontal cortex; ECT: electroconvulsive therapy; F3: left dorsolateral prefrontal cortex; F4: right dorsolateral prefrontal cortex; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation

Table 2. rTMS-associated change of clinical MDD assessment outcome before and after treatment.

Assessment scales	Pre-rTMS			Post-rTMS			Paired t-test <i>P</i> value
	N	Mean	SD	N	Mean	SD	
MADRS	53	28.1	7.3	53	20.7	10.1	0.0001 ^a
CGI-S	52	4.6	0.8	52	3.3	1.2	0.0001 ^a
DASS-21 total scores	51	67.3	24.6	51	49.6	28.0	0.0001 ^a

^a Independent t-test: *P* < 0.001

CGI-S: Clinical Global Impressions-Severity; DASS-21: Depression Anxiety and Stress Scale-21; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation

Table 3. rTMS-associated change of clinical OCD assessment outcome before and after treatment.

Assessment scale	Pre-rTMS			Post-rTMS			Paired t-test <i>P</i> value
	N	Mean	SD	N	Mean	SD	
Y-BOCS	12	30.1	7.5	11	27.2	6.9	0.799

OCD: obsessive-compulsive disorder; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; Y-BOCS: Yale–Brown Obsessive Compulsive Scale

Table 4. Change of MADR score stratified by 2 subgroups.

	Session	N	Mean	SD	Standard error mean
MADRSc	≤30	19	3.8	12.3	2.8
	>30	34	9.4	9.7	1.6

MADR: Montgomery–Åsberg Depression Rating Scale; MADRSc: change of MADRS score from baseline to post-rTMS treatment; SD: standard deviation

Table 5. Clinical outcome associated with change of MADR score.

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	T	df	Sig. (2-tailed)	Mean difference	Standard error difference	95% confidence interval of the difference	
									Lower	Upper
MADRSc	Equal variances assumed	3.242	0.078 ^a	-1.8	51	0.078	-5.517	3.067	-11.68	0.641
	Equal variances not assumed			-1.7	30.69	0.103	-5.517	3.28	-12.21	1.176

^a *P* = 0.078

MADR: Montgomery–Åsberg Depression Rating Scale; MADRSc: change of MADRS score from baseline to post-rTMS treatment

alternative treatment option for treatment-resistant MDD and OCD. Patients who received more than 30 sessions of an rTMS course are more likely to have improvement in depressive symptom severity than those having less than 30 sessions.

This study showed the efficacy of rTMS, using novel neurostimulation techniques in treatment-resistant OCD and MDD. Results were consistent across naturalistic clinics using different outcome measurements, including Y-BOCS, Hamilton Depression Rating Scale (HAM-D), HAMD-17 and CGI-S. There were 44.4% of patients with OCD who responded to rTMS—this result was consistent with previous studies, which reported a response rate of 40% to 55% based on the minimal 30% to 35% reduction in Y-BOCS baseline score.^{19,37} In comparing our depression clinician-reported outcome with similar naturalist studies, the remission rate of 17% was encouraging and comparable to 3 studies: 25.5% (HAM-D)¹⁵ and 28% (HAMD-17),¹⁴ lower than 37.1% (CGI-S).¹⁷ However, the response rate of 20.8% was less robust than most studies that reported the response rates of 40.4% (HAM-D),¹⁵ 54% (HAMD-17)¹⁴ and 58.0% (CGI-S).¹⁷

The reasons for this difference remain unclear. Our treatment population displayed greater treatment resistance as evidenced by a higher proportion of failing at least 2 antidepressant trials when compared to Carpenter et al. (66.2% vs 54%). Higher baseline symptom severity and treatment resistance have been identified indicators of poor response to rTMS.¹⁸ In our study, the proportion of patients receiving prior ECT was higher than in Carpenter et al.'s sample (18.6% vs 5.2%).¹⁷ Galletly et al. found that prior ECT exposure was a significant nonresponse to rTMS.¹³ The difference in outcome measurements and the varying definitions of treatment response used highlight the need to have a standardised definition of treatment response to facilitate fair comparisons of treatment outcomes across clinics.

Consistent with above hypothesis on the need for standardised definitions, the second finding suggested that dosing additional rTMS treatment with more than 30 sessions might help more MDD patients to have a meaningful improvement. This finding disagreed with the approach to exclude non-responders from further treatment with rTMS or predict poor response to rTMS at 10 sessions at 2 weeks.²² Non-responders identified at session 10 could convert to responders with progressively longer rTMS courses administered beyond 30 sessions at a steady and slower rate.²⁷ Wilson et al. explained that daily conventional

rTMS (i.e. 30 sessions over 6 weeks) would be insufficient for late-responders with highly treatment-resistant illnesses.³¹ The average trajectory of depressive symptom changes for late responders corresponded to the rTMS course, which showed that the effectiveness of rTMS declined sharply after 10 sessions but peaked after 30 sessions.²⁷ Interestingly, this finding differs from ECT dosing (another form of neuromodulation therapy). Chan et al. suggested that the largest clinical improvement for most patients would be between the third and sixth ECT sessions with a plateau of treatment response after 6 sessions.³⁸ rTMS efficacy was dose-dependent. Robust dose and response effects were further supported by 2 studies: dosing an additional 6 sessions in non-responders after completing 20 treatment sessions resulted in a 61% response rate.³⁹ Preservation rTMS was used as a safe and effective strategy to sustain positive outcomes after completing an acute course of rTMS.³¹ This study's results could help prevent the premature termination of rTMS treatment and potentially affect the clinical practice of rTMS dosing. However, not all patients had access to additional/preservation rTMS due to travel, cost, rTMS capacity or other constraints. These factors could confound the treatment outcome beyond 30 sessions. Future interventions, such as accelerated rTMS modalities, addressed this practical issue by adding more sessions and could theoretically expedite treatment response time.²⁴

The strengths of this study include the use of clinician-rated and self-report scales to determine rTMS outcomes. The dual-source measurement outcomes offer a complimentary source of confidence in our findings, directly and indirectly reflecting the patient's mood and general condition pre- and post-rTMS treatment.

One of the limitations was missing data. The team could not ensure a complete assessment of secondary outcome measurement at the end of acute rTMS treatment. The sample size of 58 (MDD) and 13 (OCD) resulted in insufficient power to detect any significant demographic and clinical predictors of rTMS response. Another limitation was that patients continued their concurrent psychiatric medication unchanged during the rTMS course. Certain drugs (i.e. benzodiazepine, lithium) that could potentially undermine rTMS response had been screened by rTMS psychiatrists and withheld before pursuing rTMS treatment. However, similar to other observational studies, we did not control the factors that were known to attenuate rTMS efficacy, such as concomitant antipsychotic use in depression with psychotic features.

Further analysis of responders and non-responders to rTMS treatment should be conducted systematically by comparing their sociodemographic and clinical predictors. Doing so will facilitate the appropriate selection of rTMS patients as well as the optimisation of rTMS techniques (e.g. individual neuro-navigation) to have an optimal clinical outcome. Future studies need to characterise the clinical features of late responders.

CONCLUSION

In summary, at a group level, patients with MDD and OCD in Southeast Asia responded well to rTMS treatment. Patients who received longer rTMS (≥ 30 sessions) may be associated with better antidepressant outcomes. Additionally, the result of this study supports revising long-term rTMS subsidies for treatment-resistant depression to cover at least 30 sessions to better address clinical needs.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

The manuscript was approved by the National Healthcare Group's Domain Specific Review Board (Reference no.: 2023/00415).

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REFERENCES

- McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry* 2018;79:2-3.
- Perera MPN, Mallawaarachchi S, Miljevic A, et al. Repetitive Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Meta-analysis of Randomized, Sham-Controlled Trials. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2021;6:947-60.
- Albert U, Aguglia A. Treatment-Resistant Obsessive-Compulsive Disorder (OCD): Current Knowledge and Open Questions. *Clin Neuropsychiatry* 2013;10:19-30.
- Ho RCM, Mak KK, Chua ANC, et al. The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. *Expert Rev Pharmacoecon Outcomes Res* 2013;13:549-59.
- Subramaniam M, Abdin E, Vaingankar JA, et al. Minding the treatment gap: results of the Singapore Mental Health Study. *Soc Psychiatry Psychiatr Epidemiol* 2020;55:1415-24.
- World Health Organization. World health statistics 2019: Monitoring health for the SDGs, sustainable development goals. <https://www.who.int/publications/i/item/9789241565707>. Accessed 12 August 2023.
- Rush JA, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905-17.
- George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. *Am J Psychiatry* 2011;168:356-64.
- Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. *Can J Psychiatry* 2016;61:561-75.
- Karasu B, Universities Y, Wang P, et al. Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision). *Am J Psychiatry* 2000;157:1-45.
- Academy of Medicine, Singapore. Practice Guidelines I Repetitive transcranial magnetic stimulation in the treatment of major depressive disorder, 2018. [https://www.ams.edu.sg/view-pdf.aspx?file=media%5C4381_fi_752.pdf&ofile=Guidelines+for+rTMS+Treatment+of+Major+Depressive+Disorder+20180522+\(fin....pdf](https://www.ams.edu.sg/view-pdf.aspx?file=media%5C4381_fi_752.pdf&ofile=Guidelines+for+rTMS+Treatment+of+Major+Depressive+Disorder+20180522+(fin....pdf). Accessed 13 August 2024.
- Tan XW, Oon LK, Tsang YYT, et al. A Pilot Study of Switching Electroconvulsive Therapy for Patients with Treatment-Resistant Schizophrenia or Mood Disorder. *J ECT* 2021;37:202-6.
- Galletly CA, Clarke P, Carnell BL, et al. A clinical repetitive transcranial magnetic stimulation service in Australia: 6 years on. *Aus N Z J Psychiatry* 2015;49:1040-7.
- Dowling NL, Bonwick R, Dharwadkar NP, et al. Repetitive transcranial magnetic stimulation for major depression: A naturalistic observational study in an Australian private hospital. *Psychiatry Res* 2020;291:113275.
- Griffiths C, O'Neill-Kerr A, Millward T, et al. Repetitive transcranial magnetic stimulation (rTMS) for depression: outcomes in a United Kingdom (UK) clinical practice. *Int J Psychiatry Clin Pract* 2019;23:122-7.
- Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation. *J Affect Disord* 2020;277:65-74.
- Carpenter LL, Janicak PG, Aaronson ST, et al. Transcranial magnetic stimulation (TMS) for major depression: A multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depress Anxiety* 2012;29:587-96.
- Fitzgerald PB, Hoy KE, Anderson RJ, et al. A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION. *Depress Anxiety* 2016;33:746-53.
- Rostami R, Kazemi R, Jabbari A, et al. Efficacy and clinical predictors of response to rTMS treatment in pharmacoresistant obsessive-compulsive disorder (OCD): a retrospective study. *BMC Psychiatry* 2020;20:372.
- Zhao YJ, Tor PC, Khoo AL, et al. Cost-Effectiveness Modeling of Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy for Treatment-Resistant Depression in Singapore. *Neuromodulation* 2018;21:376-82.
- Kaster TS, Downar J, Vila-Rodriguez F, et al. Trajectories of Response to Dorsolateral Prefrontal rTMS in Major Depression: A THREE-D Study. *Am J Psychiatry* 2019;176:367-75.

22. Feffer K, Lee HH, Mansouri F, et al. Early symptom improvement at 10 sessions as a predictor of rTMS treatment outcome in major depression. *Brain Stimul* 2018;11:181-9.
23. Agency for Care Effectiveness. Repetitive transcranial magnetic stimulation for adults with treatment-resistant major depressive disorder. <https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/details/repetitive-transcranial-magnetic-stimulation-for-adults-with-treatment-resistant-major-depressive-disorder>. Accessed 13 August 2024.
24. Tan XW, Abdin E, Tor PC. Accelerated transcranial magnetic stimulation (aTMS) to treat depression with treatment switching: study protocol of a pilot, randomized, delayed-start trial. *Pilot Feasibility Stud* 2021;7:104.
25. Tor PC, Gálvez V, Goldstein J, et al. Pilot Study of Accelerated Low-Frequency Right-Sided Transcranial Magnetic Stimulation for Treatment-Resistant Depression. *J ECT* 2016;32:180-2.
26. Leon AC. Evaluation of psychiatric interventions in an observational study: issues in design and analysis. *Dialogues Clin Neurosci* 2011;13:191-8.
27. Hutton TM, Aaronson ST, Carpenter LL, et al. Dosing transcranial magnetic stimulation in major depressive disorder: Relations between number of treatment sessions and effectiveness in a large patient registry. *Brain Stimul* 2023;16:1510-21.
28. Martin DM, Gálvez V, Lauf S, et al. The Clinical Alliance and Research in Electroconvulsive Therapy Network: An Australian Initiative for Improving Service Delivery of Electroconvulsive Therapy. *J ECT* 2018;34:7-13.
29. Bakker N, Shahab S, Giacobbe P, et al. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. *Brain Stimul* 2015;8:208-15.
30. Feffer K, Fettes P, Giacobbe P, et al. 1Hz rTMS of the right orbitofrontal cortex for major depression: Safety, tolerability and clinical outcomes. *Eur Neuropsychopharmacol* 2018;28:109-17.
31. Wilson S, Croarkin PE, Aaronson ST, et al. Systematic review of preservation TMS that includes continuation, maintenance, relapse-prevention, and rescue TMS. *J Affect Disord* 2022;296:79-88.
32. Quilty LC, Robinson JJ, Rolland JP, et al. The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res* 2013;22:175-84.
33. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive-Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;46:1006-11.
34. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edmont)* 2007;4:28-37.
35. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther* 1995;33:335-43.
36. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 2006;31:1841-53.
37. Singh S, Kumar S, Gupta A, et al. Effectiveness and Predictors of Response to 1-Hz Repetitive Transcranial Magnetic Stimulation in Patients With Obsessive–Compulsive Disorder 2019;35:61-6.
38. Chan CYW, Abdin E, Seow E, et al. Clinical effectiveness and speed of response of electroconvulsive therapy in treatment-resistant schizophrenia. *Psychiatry Clin Neurosci* 2019;73:416-22.
39. Yip AG, George MS, Tendler A, et al. 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. *Brain Stimul* 2017;10:847-9.