

Transcranial magnetic stimulation in psychiatry: A Singapore perspective

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The use of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) has not been described in Singapore. Reports on the effectiveness of rTMS in populations outside of Western countries are also limited. Thus, Ye et al.'s study on the naturalistic outcomes of rTMS treatment is important in the Asian context.¹ The lifetime prevalence of depression in Singapore is 6.3%.² It has been estimated that 30%–60% of patients with MDD do not respond to a first-line antidepressant, whereas 40% do not respond to a second-line antidepressant. Treatment resistant depression (TRD) is a term often used when a patient has failed to respond to 2 different antidepressants, with adequate adherence for a duration of 4–8 weeks. Further trials of antidepressant medication result in diminishing response rates and prolonging illness duration.³ Options for TRD include continued trials of different medications—utilising switching, augmentation or combination approaches and using psychotherapy and/or non-invasive neurostimulation techniques, such as rTMS and electroconvulsive therapy (ECT). While ECT is recognised as the most effective non-invasive neurostimulation treatment, studies have increasingly demonstrated that rTMS is more cost effective⁴ and has demonstrated superiority to switching antidepressants.⁵ In Singapore, the College of Psychiatrists endorsed the use of rTMS for MDD in 2015 and OCD in 2018. The Institute of Mental Health (IMH) has the largest psychiatric rTMS service in Singapore.

In Ye et al.'s observational study published in this issue of the Annals, 53 patients with MDD received rTMS treatment. Response (20.8%) and remission (17.0%) rates for depression based on MADRS mean scores were lower than expected. The largest (n=5010) naturalistic study to date reported higher response (57.7%) and remission (27.7%) rates based on self-report (PHQ-9).⁶ Another naturalistic study (n=435) that focused only on TRD patients also reported higher response (31.0%) and remission (22.8%) rates based on clinician rating (MADRS).⁷ The meta-analysis of randomised sham-controlled trials showed that active rTMS (n=840) had 39.7% response and 35.7% remission rates for TRD, while response and remission rates using sham rTMS were 13.7 and 8.4%, respectively.⁸

Higher levels of treatment resistance and greater depression severity in the current episode may result in lower treatment response. In Ye et al.'s cohort, not all MDD patients had TRD, and their average depression severity score (MADRS=28.1) pre-treatment was only in the moderate category (MADRS 20–34) and not severe category (MADRS 35–60). However, a large proportion of patients failed to respond to 3 or more antidepressants. Whether this cohort had psychotic features or other comorbidities that affected treatment outcome is unknown; hence, the authors could have described the clinical characteristics of patients in greater detail. Only 32/53 (60.4%) of MDD patients received rTMS over the left dorsolateral prefrontal cortex, which is currently the only rTMS target site for MDD that is approved by the US Food and Drug Administration (FDA). Other target sites for MDD are considered off-label. The treatment coil used in this study is a double-cone figure-8 (Fo8) coil with angled wings, which is a deviation from the flat Fo8 coil used in the MagPro system that is FDA-approved for MDD. Angled Fo8 coils have different depths of decay and focality compared to conventional flat Fo8 coils. These technical deviations should be examined closely by the authors in future to determine whether they have a bearing on treatment outcome.

Ye et al.'s study involved a small number (n=13) of OCD patients. The authors defined treatment response as achieving at least 20% reduction in clinician-rated OCD severity score (Yale–Brown Obsessive Compulsive Scale [Y-BOCS]). Clinical trials typically define response as a 30%–35% reduction in the Y-BOCS score. Had the authors used the conventional definition of response, the actual response rates would have been lower than reported. The low treatment efficacy was also observed in the mean change of severity scores. No statistically significant difference was detected between the pre and post-treatment scores. The study did not specify the exact stimulation site or stimulation frequency for OCD. The level of treatment resistance in OCD patients was also not clearly presented, which makes it difficult to understand why treatment efficacy was low in this

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study. A larger cohort will be needed to determine whether this is a spurious observation.

This study reported that the subgroup of patients with less than 30 sessions of rTMS had a higher proportion of non-responders. Although the authors suggested that more than 30 sessions of rTMS may be helpful for better response, this was not substantiated by their subgroup analysis of mean difference in pre and post-treatment scores. This observation is limited by several factors. First, not all patients could afford to have an acute course of rTMS with more than 30 sessions, as the financial subsidy by the Ministry of Health in Singapore is only available for the first 24 treatment sessions. Second, the continuation of treatment beyond 30 sessions was only offered to patients who had >25% MADRS improvement at session 30. Some evidence suggests that patients can continue to benefit from more than 30 sessions of rTMS even if they did not experience significant improvement in the first 30 sessions.⁹ Third is the hospital/clinic-based nature of rTMS treatment. Having to commute daily to and from a treatment centre over a longer course of treatment may be difficult for an individual who has MDD.

Despite the limitations, Ye et al.'s study highlighted an interesting therapeutic field that is rapidly progressing. rTMS treatment can be shortened using accelerated protocols where multiple treatment sessions are performed in 1 day instead of the standard 1 session per day.¹⁰ This significantly reduces the total number of days required for a course of treatment that could improve both treatment uptake and adherence. Neuronavigation techniques based on structural and functional brain imaging are being utilised for more precise targeting and individualised treatment, resulting in enhanced treatment efficacy.¹¹ Access to rTMS in Singapore is no longer a barrier to treatment, as rTMS service is now provided by the public and private healthcare sectors. The financial burden of rTMS treatment has been alleviated by recent improvements to Medisave and insurance claim processes.

Given the known prevalence of MDD in Singapore and the estimates of TRD, Ye et al. investigated a relatively small number of patients who underwent rTMS in IMH over a 5-year period. rTMS likely remains underutilised in Singapore. There is room for improvement in raising public awareness towards this form of neurostimulation treatment. Psychiatrists should also gain more exposure to rTMS use. Training in rTMS is being proposed to be part of the psychiatry residency programme, and exploring the delineation of interventional psychiatry might increase visibility and enhance

expertise. Further work could be done to strengthen collaboration in the areas of clinical service, research and education across healthcare clusters to position Singapore as a regional centre of excellence for rTMS.

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.

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REFERENCES

1. Ye SJ, Lu LS, HH Phu et al. Repetitive transcranial magnetic stimulation for major depression and obsessive-compulsive disorders in Singapore. *Ann Acad Med Singap* 2024;53:471-80.
2. Subramaniam M, Abdin E, Vaingankar JA, et al. Tracking the mental health of a nation: Prevalence and correlates of mental disorders in the second Singapore mental health study. *Epidemiol Psychiatr Sci* 2019;29:e29.
3. Tor PC, Amir N, Fam J, et al. A Southeast Asia Consensus on the Definition and Management of Treatment-Resistant Depression. *Neuropsychiatr Dis Treat* 2022;18:2747-57.
4. 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.
5. Papakostas GI, Trivedi MH, Shelton RC, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. *Mol Psychiatry* 2024.
6. 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.
7. Bouaziz N, Laidi C, Bulteau S, et al. Real world transcranial magnetic stimulation for major depression: A multisite, naturalistic, retrospective study. *J Affect Disord* 2023; 326:26-35.
8. Vida RG, Sághy E, Bella R, et al. Efficacy of repetitive transcranial magnetic stimulation (rTMS) adjunctive therapy for major depressive disorder (MDD) after two antidepressant treatment failures: meta-analysis of randomized sham-controlled trials. *BMC Psychiatry* 2023;23:545.
9. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial Magnetic Stimulation in the Acute Treatment of Major Depressive Disorder: Clinical Response in an Open-Label Extension Trial. *J Clin Psychiatry* 2008;69:441-51.
10. 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.
11. Temasek Foundation. Singapore Pilots Personalised Transcranial Magnetic Stimulation for Treatment-Resistant Depression, 12 April 2024. <https://temasekfoundation.org.sg/news/media-releases/singapore-pilots-personalised-transcranial-magnetic-stimulation-for-treatment-resistant-depression>. Accessed 14 June 2024.