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Accelerated repetitive transcranial magnetic stimulation in the treatment of depressive disorder resistant to a course of antidepressant medication

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Abstract

Aims It is generally known that 30% of Major depressive disorder (MDD) patients do not respond to traditional pharmacological and psychosocial therapy. Transcranial magnetic stimulation (TMS), introduced first in 1985, was a non-invasive neural network research method. Later, repetitive Transcranial Magnetic Stimulation (rTMS) was approved by the FDA to treat treatment-resistant depression (TRD) in 2008. Over the past two decades, rTMS has been extensively developed using various protocols in order to stimulate superficial brain nerve cells non-invasively. We planned to see if high-frequency accelerated left prefrontal rTMS can improve symptoms of treatment resistant depression given its convenience it provides by having patients for fewer treatment sessions.

Methods A total of 25 patients were enrolled in the study. Inclusion criteria were age between 18 and 60 and a history of at least one failed treatment with antidepressants. The treatment was conducted over six days scattered over three weeks and each day consisted of three 30-minute sessions (83, 83, and 84 trains for each session). The sessions were separated with 15-minute breaks. rTMS protocol: 120% of the motor threshold and frequency of 10 Hz. Consisting of 2.4 s trains with an intertrain interval of 15-seconds.

Result The study included 25 individuals (male: 12/13) with an average age of 36.88 ± 10.61. We compared outcome indicators at baseline and week three after confirming the normality of the data. After three weeks, Hamilton Depression Rating Scale and Clinician Global Impression showed a substantial improvement. There was a remission rate of 24% (6/25) and a response rate of 52% (13/25).

Conclusion This work adds to the evidence that rTMS can treat TRD and shows that a more convenient high-frequency accelerated rTMS can improve symptoms in treatment resistant depression.

Keywords Depression, Stimulation, rTMS, Antidepressant medication

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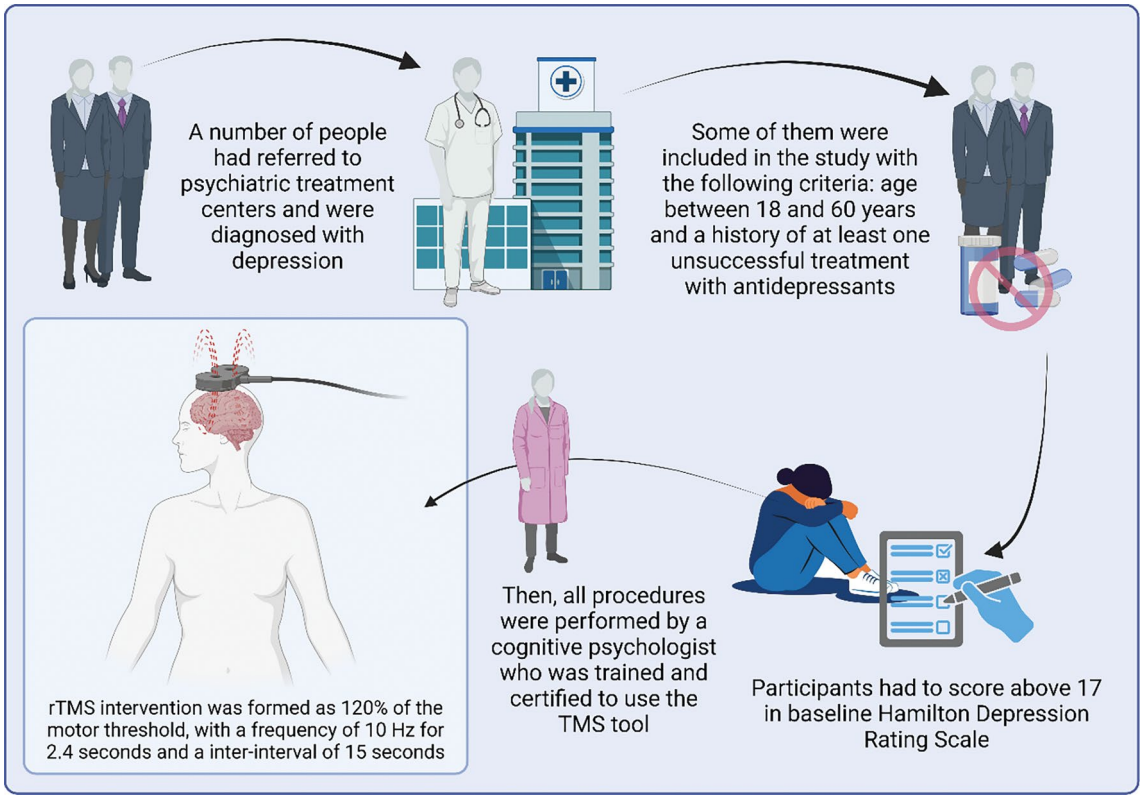
Graphical Abstract



Introduction

Major depressive disorder (MDD) is a prevalent and incapacitating condition characterized by a significant non-response rate to treatment; roughly 30% of MDD patients fail to respond to conventional pharmaceutical and psychosocial interventions [1]. Treatment-resistant depression (TRD) exerts a considerable burden on individuals and their families, resulting in substantial healthcare expenses related to its management and treatment.

Transcranial magnetic stimulation (TMS) was initially introduced in 1985 as a non-invasive technique for investigating brain networks [2]. In 2008, the US Food and Drug Administration (FDA) approved repeated transcranial magnetic stimulation (rTMS) for the management of treatment-resistant depression (TRD), defined as major depressive disorder (MDD) in adult patients who have not achieved satisfactory improvement from at least one prior antidepressant medication at or above the minimal effective dose and duration during the current episode, following favorable outcomes from clinical trials [3–5]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of stimulating nerve cells in superficial regions of the brain that has been intensively developed over the past two decades. Studies utilizing focal stimulation of the dorsolateral prefrontal cortex (DLPFC) for the treatment of depression have consistently demonstrated positive outcomes, which have been reported in several meta-analyses [6, 7]. rTMS treatment is generally well tolerated, with a very low incidence of treatment-emergent adverse effects [8]. The use of accelerated Deep TMS with the H1 Coil for Major Depressive Disorder provides patients with treatment-resistant MDD a significant likelihood of achieving remission with fast onset and enduring efficacy [9].

Conventional rTMS methods typically require daily sessions over multiple weeks, potentially restricting access for employed patients or those who must travel significant distances to a treatment facility. In response to these issues, expedited TMS techniques have been devised to reduce treatment duration. These expedited protocols employ high-frequency stimulation at 10–20 Hz, in conjunction with rapid stimulation patterns like theta burst stimulation (iTBS), facilitating a more condensed administration of pulses at diminished time intervals [10]. Stanford Intelligent Accelerated Neurotherapy (SAINT) is an exceptionally swift technique that employs high-frequency stimulation to administer 10,000 pulses throughout multiple daily sessions, demonstrating encouraging outcomes in the rapid alleviation of depressive symptoms, including in individuals with

severe depression [11, 12]. There are other studies showing a more rapid improvement of depressive symptoms with no significant adverse effects using various accelerated methods [13–17].

Notwithstanding these advancements, numerous pacing protocols continue to exhibit significant diversity in pulse frequency, duration, and stimulation objectives, with ongoing endeavors aimed at identifying optimal parameters to improve treatment outcomes in treatment-resistant depression (TRD). This work is a replication of Fitzgerald PB et al. (2018) study that employs high-frequency left prefrontal rTMS (10 Hz) with a daily administration of 10,500 pulses, grounded in evidence suggesting that an increased pulse dose may enhance neuroplasticity and therapeutic results [13] with much less discomfort [10]. This method also aligns with the objective of delivering a swifter and more accessible therapy option for patients with urgent requirements, particularly those facing serious suicidal ideation necessitating rapid intervention [18]. While the conventional rTMS protocol requires 20 clinic visits over four weeks, which can be time-consuming, the accelerated three-week protocol used in this study reduces this to six visits while delivering the same total pulse count. Additionally, conventional protocols may be associated with a slower rate of response, which could impact patients' daily functioning, work, and overall well-being. In some cases, delayed symptom improvement may also contribute to increased distress. The use of an accelerated protocol aims to enhance feasibility and potentially provide a more timely therapeutic benefit while maintaining the effectiveness of treatment.

Here again, what distinguishes this study from the standard FDA approved protocol, is the use of high pulses, 10,500 pulses in one day repeated for six days over three weeks. This study is to evaluate the effectiveness of high-frequency rTMS on the left frontal lobe in patients demonstrating resistance following medication. This study sought to evaluate the efficacy of a 6 days/3 weeks high-dose, intensive rTMS program in providing rapid symptom relief and its potential as a viable option for patients refractory to conventional antidepressant treatments.

Materials and methods

Subjects

A total of 25 patients were enrolled in the study. All subjects were referred by psychiatrists. The diagnosis was also confirmed by a structured diagnostic interview for DSM-V. Inclusion criteria were age between 18 and 60 and a history of at least one failed treatment with antidepressants. Participants had to score above 17 on the baseline Hamilton Depression Rating Scale. Participants with a history of seizures and those taking any medications that lower seizure thresholds or have any ferromagnetic material in the body were excluded from the study. Pregnant women and individuals with comorbid psychiatric disorders were also excluded.

Procedures

All procedures were conducted by a cognitive psychologist who was trained and certified to use TMS machine. All sessions were conducted under the careful supervision of the psychiatrist and the study's PI. The TMS intervention was administered over a three-week period, consisting of six treatment days in total. Each treatment day included three sessions, resulting in a total of 18 sessions. The patient visited the unit three times in the first week, twice in the second week, and once in the third week for treatment and received treatment thrice daily (Fig. 1).

rTMS protocol

We evaluated the Resting Motor Threshold (RMT) using a visual observation method. The RMT was defined as the lowest stimulation intensity that produced a visible muscle contraction in the target muscle in at least 50%

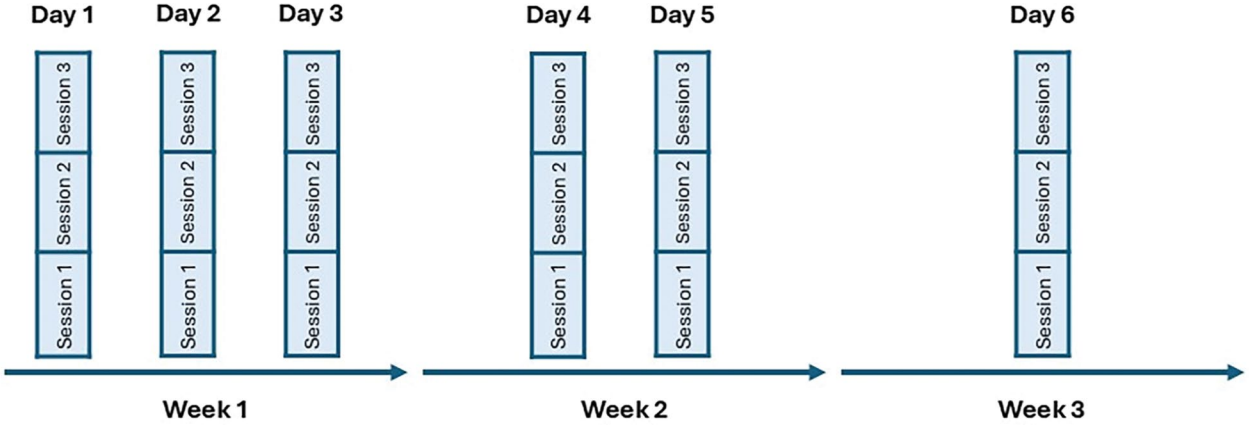


Fig. 1 rTMS sessions during 3 weeks of intervention

Table 1 Comparison of outcome measures at baseline and week 3

	Baseline	Week 3	95% Confidence Interval of the Difference	*P* Value
HDRS	26.56 ± 9.35	12.32 ± 5.87	(10.49–17.98)	0.000
CGI	5.68 ± 0.85	2.48 ± 1.12	(2.84–3.55)	0.000

HDRS: Hamilton depression rating scale

CGI: Clinician global impression

of trials. This assessment was performed manually without the use of EMG recordings. The motor threshold was evaluated once per week throughout the study.

For localization we followed the standard manual procedure [10]. First, the optimal site for activating the abductor pollicis brevis (APB) muscle in the opposite hand was identified by stimulating the corresponding motor cortical region with a supra-threshold intensity. This location was then marked on the scalp. Next, a point 6 cm anterior to this marked site was measured along the scalp surface.

rTMS intervention was performed to the left DLPFC using 120% of the motor threshold, with a frequency of 10 Hz for 2.4 s and inter–intervals of 15 s. The treatment sessions lasted for three 30-minute sessions (83, 83, and 84 train) with a 15-minute interval between sessions [10]. The patient received 10,500 pulses in each daily session (a total of 63,000 pulses for the whole protocol).

Patients continued to take their prescribed medications while receiving rTMS treatment.

Outcome measures

All patients were assessed initially and at the end of the treatment at week 3 using the Hamilton Depression Rating Scale (HDRS) and Clinician Global Impression. Both measures are translated and validated in the Persian language [19]. The response rate was defined as at least a 50% reduction in the score of HDRS, and remission rate was defined as scoring below 7 in HDRS.

Statistical analysis

IBM SPSS version 26 was used to perform statistical analyses. The level of significance was determined to be $P < 0.05$. As the One-Sample Kolmogorov-Smirnov Test revealed an abnormal distribution of variables, the non-parametric Wilcoxon Signed Ranks Test was used to compare data before and after an intervention.

Ethical considerations

Written informed consent was obtained from all subjects before enrollment in the study. The study protocol was approved by the local ethics review committee of the Tehran University of Medical Sciences.

Results

A total of 25 patients (F/M: 12/13) with a mean age of 36.88 ± 10.61 were enrolled in the study.

After establishing the normality of data, outcome measures were compared at baseline and week 3. As it is shown, a significant improvement was seen in HDRS and Clinician Global Impression (CGI) after 3 weeks. The response rate was 52% (13/25) and the remission rate was 24% (6/25) (Table 1).

For the next step, we conducted generalized linear model repeated measures to explore the effects of age and gender and define effect sizes. The difference in HDRS and CGI was neither affected by age nor gender (Table 2).

Discussion

This study investigates the use of high-frequency accelerated left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a treatment for patients with treatment-resistant depression (TRD) who have not responded to antidepressant medication.

Our findings indicate a statistically significant improvement in both the Hamilton Depression Rating Scale (HDRS) and Clinician Global Impression (CGI) scores after the three-week rTMS intervention, which favors the

Table 2 General linear model, repeated measures of HDRS and CGI with age and gender as covariates

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
HDRS	314.273	1	314.273	8.321	0.009	0.274
HDRS * Age	8.388	1	8.388	0.222	0.642	0.010
HDRS * Gender	156.839	1	156.839	4.153	0.054	0.159
Error (HDRS)	830.907	22	37.768			
CGI	8.608	1	8.608	23.826	0.000	0.520
CGI * Age	0.895	1	0.895	2.477	0.130	0.101
CGI * Gender	0.308	1	0.308	0.852	0.366	0.037
Error (CGI)	7.948	22	0.361			

HDRS: Hamilton depression rating scale

CGI: Clinician Global Impression

No side effects were reported by patients. There were no dropouts as well

potential effectiveness of accelerated rTMS in alleviating depressive symptoms.

Accelerated rTMS has emerged as a promising treatment protocol, enhancing patient compliance. The issue of compliance is of paramount significance as in todays' large metropolitan cities that would hinder rTMS treatment given quite a few numbers of sessions needed. It's important to note that most studies investigating accelerated rTMS suffer from limitations such as small sample sizes, short follow-up periods, and a lack of sham-controlled groups [20–22].

Reviewing 23 studies, Caulfield and colleagues found that accelerated rTMS yielded an average response rate of 42.4% and a remission rate of 28.4% for depression. Notably, this approach showed side effect rates comparable to standard rTMS [20]. Based on a recent review and meta-analysis changes in depressive symptoms were found in 6 randomized clinical trials and 5 open-label studies and changes in suicidal ideation were reported in 2 RCTs. The cumulative effect size derived from 3 RCTs was 0.39 (95% CI 0.005–0.779) was found. Accelerated rTMS resulted in a significant mean change in the Hamilton Depression Rating Scale (HDRS) of 6.28 (± 0.78 SE) compared to 3.63 (90% CI ± 0.74 SE) for the sham group, with the accelerated rTMS group showing superior improvement ($p = 0.041$) [23].

Miron et al. examined the effectiveness of a one-week (5 days) accelerated (8 sessions per day) course of 1 Hz rTMS over the right dorsolateral prefrontal cortex on 30 patients conducting a single arm study. Results indicated that accelerated rTMS is well-tolerated and safe, leading to a 33% response rate at week 1 and an increase to 43% at week 4 [24]. Similarly, a feasibility study on elderly depressed patients found accelerated rTMS (5 sessions per day; 4 consecutive days) to be effective in improving depression with a response rate of 40% and remission rate of 20% in 10 patients [25].

Fitzgerald PB and colleagues reported equal efficacy between accelerated rTMS ($n = 58$) with 3 treatments per day over 3 days in week 1, 3 treatments over 2 days in week 2, and 3 treatments on a single day in week 3 and standard rTMS ($n = 57$). No adverse effects were reported by patients receiving accelerated rTMS despite showing higher treatment discomfort [10].

In a retrospective study, Modirrusta et al. compared twice daily with once daily high-frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex. Patients receiving twice daily rTMS showed a greater response rate over a shorter period compared to those receiving once daily rTMS (82.4% vs. 52.6%) [26]. Evidence of tolerability and a higher pace of improvement in accelerated rTMS have been repeated in some studies [27]. Schulze et al. suggested that there is a consistent relationship between the pace of improvement and number of cumulative sessions.

Reaching a faster improvement could be critical when managing acute conditions like suicidal ideations. A sham-controlled study using 20 accelerated intermittent Theta Burst Stimulation (iTBS) over DLPFC in 4 days in treatment-resistant unipolar depressed patients demonstrated a decrease of suicide risk following accelerated iTBS, without statistically significant difference between the effect of active and the sham treatment. It should be noted that participants were antidepressant-free during the study. The anti-suicidal effect lasted up to 1 month after baseline, and none of the iTBS-treated patients committed suicide until 6 months after treatment [28].

Limitation

The small sample size and lack of sham controls may affect the generalizability of the results. Additionally, the study's short duration and lack of a long-term follow-up make it necessary to conduct more extensive research to confirm the sustained effectiveness and safety of high-frequency accelerated rTMS. Furthermore, we did not assess the potential influence of medications used by patients on motor threshold and treatment response. Our sample included a near-equal distribution of male and female participants, which may not fully reflect real-world gender ratios in depression. Although gender did not significantly impact treatment response, further research with larger, more representative samples is needed to explore potential gender differences in treatment efficacy.

Conclusion

Overall, this study contributes to the growing body of evidence regarding rTMS as a treatment for TRD and suggests that high-frequency accelerated rTMS could be a promising approach to explore further in the field of depression treatment. Its potential for faster results and the absence of significant age or gender-related differences could make it a flexible option for a wide range of patients. Further research with a larger sample size and long-term follow-up is needed to confirm and extend our findings.

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Author contributions

M.M. data analysis and manuscript review and editing. A.F. writing original draft, data collection, and analysis. A.H-H. writing the original draft, manuscript review, and editing. J.A-r. supervised the thesis and experimental design.

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Data availability
Data will be made available on request.

Declarations

Ethics approval and consent to participate
Human ethics have been observed, and consent to participation has been obtained from all participants in this research. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The Tehran University of Medical Sciences Ethics Committee confirmed this investigation (ethics code: IR.TUMS.MEDICINE.REC.1401.666).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Fava M, Davidson KG. Definition and epidemiology of Treatment-Resistant depression. Psychiatr Clin North Am. 1996;19(2):179–200.
2. Barker AT, Jalinous R, Freeston IL. Non-Invasive magnetic stimulation of human motor cortex. Lancet. 1985;325(8437):1106–7.
3. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. Biol Psychiatry. 2007;62(11):1208–16.
4. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, Strong MJ, Sharma R, Rosen C, Viana M. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry. 2002;51(8):659–67.
5. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehavioral Reviews. 2018;92:291–303.
6. Schutter DJLG. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med. 2008;39(1):65–75.
7. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):19531.
8. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008–39.
9. Roth Y, Hanlon CA, Pell G, Zibman S, Harmelech T, Muir OS, MacMillan C, Prestley T, Purselle DC, Knightly T. Real world efficacy and safety of various accelerated deep TMS protocols for major depression. Psychiatry Res. 2023;328:115482.
10. Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology. 2018;43(7):1565–72.
11. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, Nejad R, Pankow H, Choi E, Aaron H. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. Am J Psychiatry. 2020;177(8):716–26.
12. Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, Cherian K, Hawkins J, Scherrer KH, Vyssoki B. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain. 2018;141(3):e18–18.
13. Baeken C, Vanderhasselt M-A, Remue J, Herremans S, Vanderbruggen N, Zeeuws D, Santermans L, De Raedt R. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. J Affect Disord. 2013;151(2):625–31.
14. Hadley D, Anderson BS, Borckardt JJ, Arana A, Li X, Nahas Z, George MS. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for Treatment-Resistant depression in a clinical setting. J ECT. 2011;27(1):18–25.
15. Holtzheimer PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, Epstein CM. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depress Anxiety. 2010;27(10):960–3.
16. McGirr A, Van den Eynde F, Tovar-Perdomo S, Fleck MPA, Berlim MT. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. J Affect Disord. 2015;173:216–20.
17. van Rooij SJH, Arulpragasam AR, McDonald WM, Philip NS. Accelerated TMS - moving quickly into the future of depression treatment. Neuropsychopharmacology. 2023;49(1):128–37.
18. Grunebaum MF, Galfalvy HC, Choo T-H, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: A Midazolam-Controlled randomized clinical trial. Am J Psychiatry. 2018;175(4):327–35.
19. Brand S, Ahmadpanah M, Sheikhbabaei M, Haghighi M, Roham F, Jahangard L, Akhondi A, Sadeghi Bahmani D, Bajoghli H, Holsboer-Trachsler E: Validity and test–retest reliability of the Persian version of the Montgomery–Asberg Depression Rating Scale. *Neuropsychiatric Disease and Treatment* 2016, 12:603–607.
20. Caulfield KA, Fleischmann HH, George MS, McTeague LM. A transdiagnostic review of safety, efficacy, and parameter space in accelerated transcranial magnetic stimulation. J Psychiatr Res. 2022;152:384–96.
21. Rachid F. Accelerated transcranial magnetic stimulation for the treatment of patients with depression: A review. Asian J Psychiatry. 2019;40:71–5.
22. Chen L, Hudaib A-R, Hoy KE, Fitzgerald PB. Efficacy, efficiency and safety of high-frequency repetitive transcranial magnetic stimulation applied more than once a day in depression: a systematic review. J Affect Disord. 2020;277:986–96.
23. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, Croarkin PE. Accelerated TMS for depression: A systematic review and meta-analysis. Psychiatry Res. 2019;273:770–81.
24. Miron J-P, Hyde M, Fox L, Sheen J, Voetterl H, Mansouri F, Jodoin VD, Zhou R, Dees S, Mir-Moghtadaei A. Evaluation of a 5 day accelerated 1 hz repetitive transcranial magnetic stimulation protocol in major depression: a feasibility study. J Affect Disorders Rep. 2021;4:100077.
25. Dardenne A, Baeken C, Crunelle CL, Bervoets C, Matthys F, Herremans SC. Accelerated HF-rTMS in the elderly depressed: A feasibility study. Brain Stimul. 2018;11(1):247–8.
26. Modirrousta M, Meek B, Wikstrom S. Efficacy of twice-daily vs once-daily sessions of repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: a retrospective study. Neuropsychiatr Dis Treat. 2018;14:309–16.
27. Schulze L, Feffer K, Lozano C, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J. Number of pulses or number of sessions? An open-label study of trajectories of improvement for once-vs. twice-daily dorsomedial prefrontal rTMS in major depression. Brain Stimul. 2018;11(2):327–36.
28. Desmyter S, Duprat R, Baeken C, Van Autreve S, Audenaert K, van Heeringen K. Accelerated intermittent Theta burst stimulation for suicide risk in Therapy-Resistant depressed patients: A randomized, Sham-Controlled trial. Front Hum Neurosci. 2016;10:480.

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