

REMISSION AND FOLLOW-UP IN BIPOLAR DEPRESSION WITH ACCELERATED INTERMITTENT THETA BURST STIMULATION PROTOCOL

Sercan SİVLİM¹, Hayri Can ÖZDEN²,
A. Elif ANIL YAĞCIOĞLU³, Ş. Can GÜREL⁴

Dear Editor,

Transcranial Magnetic Stimulation (TMS) is used in the treatment of many mental illnesses, as well as for research in mental illnesses (Altınbaş et al. 2007, Yıldız et al. 2015). Intermittent Theta Burst Stimulation (iTBS) is a treatment protocol that is applied with 10 - 20 Hz and has a similar effect to Repetitive Transcranial Magnetic Stimulation (rTMS) (Blumberger et al. 2018). The FDA approved the standard iTBS protocol in 2018 to treat treatment-resistant depression.

Accelerated Intermittent Theta Burst Stimulation (aiTBS), on the other hand, describes protocols that include multiple iTBS sessions on a single day for 5-10 days (Cole et al. 2024). The main goal of accelerated aiTBS is to reduce the number of days required to complete the treatment process. However, according to the available evidence, there is insufficient evidence on the efficacy of both iTBS and aiTBS for bipolar depression (Cole et al. 2024, McGirr et al. 2021).

This paper presents the case of a 25-year-old female patient. Consent was obtained from the patient for the presentation of this case, but no ethics committee approval was sought. Since 2015, she has experienced depressive episodes every winter, each lasting three months and characterized by symptoms such as depressed mood, anhedonia, feelings of worthlessness, and thoughts of death, similar to her current condition. During the summers of 2015 and 2017, she had

periods hypomania marked by increased energy, reduced need for sleep, increased goal-directed activity, increased libido, and excessive spending. In other words, since 2015, the patient has experienced eight depressive episodes and two hypomanic episodes, with her mood episodes showing seasonal patterns. In this admission, the patient had depressive symptoms which developed under duloxetine 60 mg/day and lamotrigine 200 mg/day treatment and had been persisting for several months. Firstly, the patient's drug regimen was arranged. Although antidepressant, mood stabilizer, and antipsychotic combinations and 11 sessions of cognitive behavioral psychotherapy were administered in adequate doses and duration for a year and a half of follow-up, no response was obtained; either she did not benefit from the treatments or her symptoms recurred after a short period of time. When evaluated for accelerated iTBS, the patient had been on lamotrigine 400 mg/day, bupropion 300 mg/day, modafinil 100 mg/day, olanzapine 5 mg/day, and sertraline 50 mg/day for three months, but her depressive symptoms persisted.

After the evaluation, the patient's left dorsolateral prefrontal cortex location was determined anthropometrically with the F3 - Beam method (Mir-Moghtadaei et al. 2022). The accelerated iTBS protocol was performed with Neurosoft Neuro-MS/D and an angled figure-of-eight coil. Motor threshold was determined based on observation of musculus abductor pollicis brevis contraction. The resting motor threshold was determined as the lowest magnetic stimulation intensity at which stable contraction could be achieved for 10 consecutive stimulations at rest. The accelerated iTBS protocol consisted of 2-second bursts of 50 Hz triple pulses (5 Hz) and 8-second intervals, totaling 1800 pulses in one session at the 80% motor threshold. It was repeated for two weeks (10 days on weekdays only), with three sessions per day with a minimum interval of 40 minutes. During the whole treatment course, 5400 pulses per day - 54,000 pulses in total were administered. The patient's attending physician at Hacettepe University Department of Psychiatry, Center for

How to cite: Sivlim S, Özden HC, Anıl Yağcıoğlu AE ve ark. (2025) Remission and Follow-Up in Bipolar Depression with Accelerated Intermittent Theta Burst Stimulation Protocol. *Türk Psikiyatr Derg* 36:30. <https://doi.org/10.5080/u27553>

Received: 12.07.2024, **Accepted:** 29.07.2024, **Available Online Date:** 06.08.2024

¹Resident, ³Prof, ⁴Assoc. Prof., Hacettepe University Medical Faculty, Department of Psychiatry, Ankara; ²Psychiatrist, Hatay Samandağ State Hospital, Division of Psychiatry, Hatay.

Dr. Ş. Can Gürel, e-mail: scangurel@hacettepe.edu.tr

Psychiatric Interventions started to administer the Hamilton Depression Scale (HAM-D) (Hamilton 1960, Akdemir et al. 2001) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979, Kara-Özer et al. 2001) immediately before aiTBS was administered to the patient, and the scales were continued to be administered weekly during aiTBS treatment and remission. After remission, the patient continued to be examined once a month, and the same scales continued to be administered by the same physician at each visit. During the aiTBS treatment, no side effects such as headache, dizziness, drowsiness, facial tingling or facial muscle contraction were observed. There were no manic shift or epileptic seizures. At the end of two weeks of treatment, it was observed that the patient responded to the treatment (more than 50% decrease in HAM-D scale score) (Figure 1). Following the termination of the treatment, the patient's depressive symptoms continued to improve. One week after the treatment was terminated, the patient was determined to be in remission (HAM-D score < 7) (Table 1 and Figure 1).

Data on the efficacy of accelerated iTBS on depressive symptoms comes mostly from case reports of patients with unipolar depression. Studies on the efficacy of aiTBS in bipolar depression are scarce. There are open-label studies that include patients with major depression and bipolar affective disorder and report changes in depressive symptoms after administration of aiTBS. Some of these studies (Bröcker et al. 2019) reported improvement in the symptoms of patients with bipolar affective disorder, while others (Cantù et al. 2021, Williams et al. 2018) observed no improvement in symptoms. The aiTBS protocol by Bröcker et al. (2019) involves three magnetic pulses, each 20 ms apart, repeated every 200 ms (Bröcker et al. 2019). This protocol, which yielded positive results, is a treatment in which 1782 pulses are administered in each session, each lasting approximately 13 minutes, with a motor threshold of 80% to generate a 5 Hz theta rhythm on the left dorsolateral prefrontal cortex (DLPFC). It was reported that a total of 20 sessions were applied to the patients. Cantù et al. (2021) planned a three-week aiTBS protocol: three days in the first week, two days in the second week, and one day in the last

Table 1. Scores of HAM-D and MADRS Scales Administered to the Patient During Follow-Up

Date	HAM-D	Decrease in the HAM-D Scale Score %	MADRS
Before the initiation of aiTBS	21	-	28
End of the first week of aiTBS	17	19	22
End of the second week of aiTBS	10	52	20
One month after termination of aiTBS	4	81	3
Two months after termination of aiTBS	3	86	5
Three months after termination of aiTBS	3	86	5
Four months after termination of aiTBS	3	86	5
Five months after termination of aiTBS	3	86	5
Six months after termination of aiTBS	4	81	5

aiTBS: Accelerated Intermittent Theta Burst Stimulation, HAM-D: Hamilton Depression Scale, MADRS: Montgomery-Asberg Depression Rating Scale

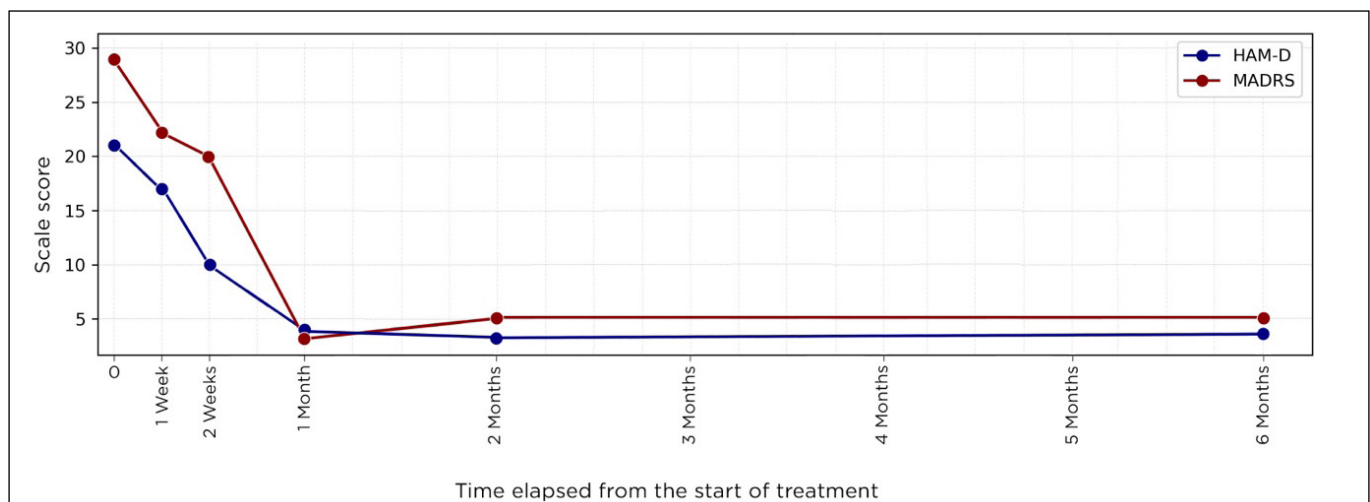


Figure 1. Scores of HAM-D and MADRS scales administered to the patient during follow-up. HAM-D: Hamilton Depression Scale, MADRS: Montgomery-Asberg Depression Rating Scale

week, for a total of six days and 18 sessions (three sessions on each stimulation day) (Cantù et al. 2021). In this study, the motor threshold was set as 80%, 30 Hz triple bursts were repeated at 5 Hz, 600 pulses were administered to the left DLPFC in each session, and 1,800 pulses were administered on each stimulation day. Williams et al. (2018) described a case where they delivered 3 pulses every 10 seconds at 90% resting motor threshold in 50-Hz bursts and 2-second intervals at 5-Hz to the left DLPFC (Williams et al. 2018). They administered 18,000 pulses per day, 10 sessions per day, for a total of 90,000 pulses over five days. Therefore, differences in the number of sessions, motor threshold, and total pulses seen in the patients' treatment protocols may have led to variations in treatment response. In a recent systematic review and meta-analysis, the authors reported that there is preliminary evidence that aiTBS is effective in the treatment of depression. However, the sample of this study included patients with both unipolar and bipolar depression (Cai et al. 2023). Some studies reviewed in this study also reported negative results regarding the efficacy of aiTBS in bipolar depression, and it was stated that these results may be related to reasons such as heterogeneity in the patient group and application protocol, and a lack of use of neuroimaging in determining the application area. The authors concluded that further studies are needed in addition to the studies with small numbers and heterogeneous groups (Cai et al. 2023).

Studies displaying negative outcomes in bipolar depression have used a motor threshold of 120% (McGirr et al. 2021). The assumption that administering a higher intensity stimulation to increase efficacy increases the neuromodulatory effect may be incorrect for iTBS. In another study, participants were stimulated at 100%, 75%, and 50% motor thresholds, and the change in cortical activity after stimulation was measured by electroencephalography (EEG), and the change in executive functions was measured by the n-backward task test (Kirchner 1958). As a result of the study, it was observed that the largest neurophysiological changes occurred when a 75% motor threshold was used (Chung et al. 2018). Therefore, in our case, maintaining a low stimulation dose may have contributed to the success of the treatment.

Another limitation of the studies on aiTBS efficacy is that the follow-ups of patients are not long-term. It is known that the antidepressant effect of aiTBS lasts at least 4 weeks (Cole et al. 2024), but there is not enough data on the course of depressive symptoms over longer periods. The presented case is notable for the emergence of a treatment response with a motor threshold of 80% and the absence of a recurrence of depressive symptoms in a follow-up period longer than six months.

In conclusion, the lack of sufficient evidence on the efficacy of aiTBS in bipolar depression or the negative results may

be due to differences in practice. Multicentered, randomized controlled trials with appropriate protocols, large sample sizes, and long-term follow-up of participants can determine whether aiTBS is effective and safe for bipolar affective disorder or not.

REFERENCES

- Akdemir A, Türkçapar MH, Örsel SD ve ark. (2001) Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. *Compr Psychiatry* 42: 161-5.
- Altınbaş K, Oral ET, Vahip S (2007) İki Uçlu Bozuklukta Transkraniyal Manyetik Uyarım Tedavisi. *Türkiye Klinikleri J Psychiatry* 29: 30-7.
- Blumberger DM, Vila-Rodriguez F, Thorpe KE ve ark. (2018) Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet Psychiatry* 391: 1683-92.
- Bröcker E, van den Heuvel L, Seedat S (2019) Accelerated theta-burst repetitive transcranial magnetic stimulation for depression in South Africa. *S Afr J Psychiatr* 25: 1346-9.
- Cai DB, Qin ZJ, Lan XJ ve ark. (2023). Accelerated intermittent theta burst stimulation for major depressive disorder or bipolar depression: A systematic review and meta-analysis. *Asian J Psychiatr* 85: 103618.
- Cantù F, Schiena G, Sciortino D ve ark. (2021) Use of 30-Hz accelerated iTBS in drug-resistant unipolar and bipolar depression in a public healthcare setting: A case series. *Front Psychiatry* 12: 798847.
- Chung SW, Rogasch NC, Hoy KE ve ark. (2018) Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. *Hum Brain Mapp* 39: 783-802.
- Cole E, O'Sullivan SJ, Tik M ve ark. (2024) Accelerated Theta Burst Stimulation: Safety, Efficacy, and Future Advancements. *Biol Psychiatry* 95: 523-35.
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23: 56-62.
- Kara-Özer S, Demir B, Tuğal Ö ve ark. (2001) Montgomery-Asberg Depresyon Değerlendirme Ölçeği: değerlendiriciler arası güvenilirlik ve geçerlilik çalışması. *Türk Psikiyatri Derg* 12: 185-94.
- Kirchner WK (1958) Age differences in short-term retention of rapidly changing information. *J Exp Psychol* 55: 352-8.
- McGirr A, Vila-Rodriguez F, Cole J ve ark. (2021) Efficacy of Active vs Sham Intermittent Theta Burst Transcranial Magnetic Stimulation for Patients With Bipolar Depression: A Randomized Clinical Trial. *JAMA Netw Open* 4: e210963.
- Mir-Moghtadaei A, Siddiqi SH, Mir-Moghtadaei K ve ark. (2022) Updated scalp heuristics for localizing the dorsolateral prefrontal cortex based on convergent evidence of lesion and brain stimulation studies in depression. *Brain Stimul* 15: 291-5.
- Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134: 382-9.
- Williams NR, Sudheimer KD, Bentzley BS ve ark. (2018): High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. *Brain* 141: e18.
- Yıldız Mİ, Temuçin Ç, Ertuğrul A (2015) Şizofreni Hastalarında Belirtilerde ve Bilişsel İşlevlerdeki Değişimin Transkraniyal Manyetik Uyarım ile Ölçülen Kortikal İnhibisyon Parametrelerindeki Değişimle İlişkisi: Sekiz Haftalık Bir İzlem Çalışması. *Türk Psikiyatri Derg* 26: 161-71.

Acknowledgment: The authors would like to thank Assistant Professor Talat Demirsöz, who provided psychotherapy for the case presented.