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Real-world case series of maintenance theta burst stimulation therapy following response to acute theta burst stimulation therapy for difficult-to-treat depression

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Abstract

Objective. Treatment and management for difficult-to-treat depression are challenging, especially in a subset of patients who are at high risk for relapse and recurrence. The conditions that represent this subset are recurrent depressive disorder (RDD) and bipolar disorder (BD). In this context, we aimed to examine the effectiveness of maintenance transcranial magnetic stimulation (TMS) on a real-world clinical basis by retrospectively extracting data from the TMS registry data in Tokyo, Japan.

Methods. Data on patients diagnosed with treatment-resistant RDD and BD who received maintenance intermittent theta burst stimulation (iTBS) weekly after successful treatment with acute iTBS between March 2020 and October 2023 were extracted from the registry.

Results. All patients (21 cases: 10 cases with RDD and 11 cases with BD) could sustain response, and 19 of them further maintained remission. In this study, maintenance iTBS did not exacerbate depressive symptoms in any of the cases, but may rather have the effect of stabilizing the mental condition and preventing recurrence.

Conclusions. This case series is of great clinical significance because it is the first study to report on the effectiveness of maintenance iTBS for RDD and BD, with a follow-up of more than 2 years. Further validation with a randomized controlled trial design with a larger sample size is warranted.

Introduction

Treatment and management of difficult-to-treat depression[1] as represented by treatment-resistant depression (TRD) are clinically challenging.[2–4] Among the difficult-to-treat depressions, clinically challenging conditions in particular include not only so-called TRD but also treatment-resistant recurrent depressive disorder (RDD)[5] and treatment-resistant bipolar disorder (BD).[6–10] The average cumulative recurrence rate for patients with major depressive disorder is estimated to be 13% at 5 years, 23% at 10 years, and 42% at 20 years,[11] and when it is limited to specialized psychiatric institutions that see a large number of patients with TRD, the recurrence rate for major depressive disorder is even higher, with an estimated 60% at 5 years, 67% at 10 years, and 85% at 15 years for patients with major depressive disorder.[12] On the other hand, observational studies of BD (follow-up period 2.1 years) reported an overall recurrence rate of approximately 55% (26%/year), and randomized controlled trails (follow-up period 1.9 years) reported an overall recurrence rate of about 39% (22%/year) in the mood stabilizer treatment group and 61% (31%/year) in the placebo group.[13] Thus, in the case of BD, more than half of the patients are likely to have a recurrence after about 2 years of follow-up, and the recurrence rate is generally higher than that of unipolar depression. As such, these data are exactly indicative of the fact that some patients with difficult-to-treat depression present with RDD and have difficulty in managing their condition, even if they respond to acute phase treatment. Furthermore, Senova et al. reported that the percentage of patients with TRD who could maintain response after responding to acute transcranial magnetic stimulation (TMS) treatment was approximately 67% after 3 months, 53% after 6 months, and 46% after 12 months of an acute course of treatment.[14]

TMS is a noninvasive treatment that stimulates specific areas of the brain with focused magnetic fields. The evidence is well established, especially for medication-resistant depression. Repetitive TMS (rTMS) treatment improves depressive symptoms in up to 70% of patients with TRD. New approaches and techniques have been developed in this area to reduce treatment time and to optimize and maximize the clinical outcomes. For example, theta burst stimulation protocols now have evidence showing that they are non-inferior to standard rTMS and offer

significant advantages in optimizing limited healthcare resources.[15] In the context of difficult-to-treat depression, previous studies have repeatedly discussed the possibility of maintenance treatment with rTMS as an effective recurrence prevention strategy for difficult-to-treat depression including TRD.[16] Prior studies have shown that maintenance TMS protocols as a recurrence prevention strategy for TRD are considerably varied, with the majority demonstrating their benefits from a clinical perspective with open-label trials and case series.[17] Indeed, to date, a total of 11 case reports and case series on maintenance TMS[4–14] have been reported from around the world (see Table 1 for details). Currently, for patients with TRD who have responded to an acute course of rTMS therapy, maintenance rTMS may be beneficial,[12, 29] regardless of protocol differences, as there are few effective and reliable noninvasive alternative treatment options available in the outpatient setting in many countries today, including Japan, other than pharmacotherapy. Furthermore, few studies have focused on and clinically evaluated the potential of maintenance TMS treatment after the successful acute TMS treatment for mood disorders such as RDD and depressive episodes of BD other than typical form of TRD.

One of the challenges currently facing clinics specializing in TMS treatment is how to provide clinically meaningful maintenance treatment and follow-up management for patients with refractory mood disorders, including RDD and BD, who have

Table 1. Summary of Case Reports and Case Series on Maintenance TMS for Depression

References	Countries of publication	Results
18	USA	This study involved seven adults with BD who responded to rTMS and received weekly rTMS for up to a year. rTMS was administered over the left prefrontal cortex at 110% motor threshold. Three subjects completed a full year of weekly rTMS, with an average HRDS of 13. The findings suggest the potential of rTMS as an adjunctive maintenance treatment for some patients with BD.
19	USA	This study applied rTMS to 10 adult patients with unipolar depression over the left prefrontal cortex and showed that 70% of the subjects experienced significant or moderate benefits, with three maintaining these benefits without additional antidepressant medication. No serious adverse events were reported, and there were no seizures in the 1831 rTMS sessions.
20	Germany	Detailed results were not available.
21	Australia	This study involved 19 patients with depression who had previously responded to rTMS treatment. After approximately 10 months, they received 30 rTMS sessions for depressive relapse. Significant improvements were observed in patients treated with both low–frequency right–sided and high–frequency left–sided rTMS. The study suggests that rTMS could be valuable in treating depressive relapse episodes, with minimal reduction in efficacy over time.
22	India	This case report emphasizes the role of rTMS in the maintenance treatment of TRD. Despite the scarcity of literature on this topic, particularly from India, the study found low dropout rates due to adverse effects. The parameter used was 100% MT, but 2000 pulses per session, total 20 sessions per episode. The patient, followed for 3 years across 4 episodes, showed symptom improvement and functional enhancement without pharmacological treatment. This underscores the potential of rTMS as a viable treatment option for TRD.
23	USA	This study evaluated the effectiveness of rTMS as a substitute for ECT in a series of 6 patients. The transition to TMS was due to ECT side effects or patient preference. All patients maintained or improved their depression status, as measured by the Beck Depression Inventory, during 3 and 6 months of TMS treatment. At the final observation (7–23 months), 4 patients maintained or improved their status, while 2 relapsed. TMS was well tolerated, with minor side effects.
24	Canada	This study describes the use of rTMS in maintaining response after ECT in 6 patients with unipolar depression or BD. rTMS was administered weekly at 120% of the resting motor threshold, with patients receiving sequential bilateral rTMS. Depressive symptoms were monitored using the Quick Inventory of Depressive Symptoms—Self–Rated. Five of the 6 patients maintained their response status for 6 to 13 months. The findings suggest that rTMS could be a key strategy in preventing relapse after ECT.
25	France	This study enrolled 59 patients with pharmacoresistant depression who responded to acute rTMS treatment. Patients either received 20 weeks of maintenance rTMS or no additional rTMS. Propensity analysis was used to examine the association between relapse rate and maintenance rTMS. At 20 weeks, the relapse rate was significantly lower in the maintenance rTMS group (37.8%) compared to the non–maintenance group (81.8%), with an adjusted hazard ratio of 0.288. The study suggests that maintenance rTMS is associated with a lower relapse rate in patients with pharmacoresistant depression.
26	USA	A retrospective review of 225 patients receiving rTMS for TRD was conducted. Sixteen patients who underwent reintroduction of rTMS were analyzed. The response to the initial rTMS course significantly correlated with the response to reintroduction and was confirmed as a significant predictor of response to reintroduction. The average change in Beck Depression Inventory scores was similar across induction and reintroduction. Most patients responded to both the initial treatment and reintroduction.
27	Australia	This 10–month prospective study investigated the effectiveness of early relapse rTMS, a protocol involving 5 rTMS sessions at monthly intervals, in managing severe relapsing depression. Thirty–nine patients received 168 series of rTMS sessions, with significant reductions in pre–/posttreatment scores observed. Post–series scores indicated remission, while pre–series scores suggested a decline in mood toward relapse. Prior to rTMS, 70% of patients were not in remission, but post–rTMS, 79% achieved remission. The findings suggest that monthly early relapse rTMS sessions can shift mood from relapse/partial remission toward remission, highlighting its potential as a management strategy for severe relapsing depression.
28	Japan	This study reported 2 cases of TRD who received 12–month maintenance rTMS after achieving remission with acute rTMS therapy. rTMS was applied at 10 Hz over the left prefrontal cortex for 6 weeks. Maintenance rTMS was applied once a week for 6 months and every other week for the next 6 months. Medications were kept stable throughout the study. Both patients remained in remission for 12 months.

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successfully responded to acute TMS treatment. In particular, treatment-resistant RDD and treatment-resistant BD have high recurrence rates and are likely to relapse weeks to months after responding to an acute course of electroconvulsive therapy (ECT)[10] as well as TMS treatment.[3] In practice, maintenance pharmacotherapy is continued in many such cases, but given that patients with medication-resistant RDD and BD undergo TMS treatment as an alternative or add-on therapy to medication, there may be little clinical rationale for just continuing maintenance pharmacotherapy, which was relatively ineffective for these patients.

With this background, this case series aimed to examine the efficacy of maintenance intermittent theta burst stimulation (iTBS) on a real-world basis by retrospectively extracting data on cases meeting the criteria described below using the clinical TMS registry data in Japan.[30] Moreover, although numerous studies have already been reported from Europe and North America on the potential of maintenance rTMS treatment for TRD,[14] no coherent report has yet been published from Japan on the treatment strategy using maintenance iTBS for such patients with RDD and BD in the context of difficult-to-treat depression. Furthermore, previous maintenance TMS studies have used maintenance treatment with rTMS, and no case series using a maintenance iTBS protocol after the successful acute treatment with iTBS has yet been reported.[28] The present study is a retrospective observational study without a control group, but we report this case series here as part of the TMS registry study because we believe it is of clinical importance in terms of a real-world study in actual clinical settings.

Methods

Case series setting

In this case series, data from patients with RDD or BD, in the context of difficult-to-treat depression, who received 15 to 30 sessions of maintenance iTBS after the successful acute course of iTBS treatment[31] at the Shinjuku-Yoyogi Mental Lab Clinic in Tokyo were extracted from the real-world clinical TMS database registry. The data included in this case series were collected between January 2020 and September 2023. Specifically, case series data of 21 outpatients (including 10 patients with RDD and 11 patients with BD type II) who had received a total of 15 to 45 sessions of acute iTBS treatment and had at least a clinical response and then transitioned to weekly (15 to 30 sessions) maintenance iTBS treatment were extracted and analyzed retrospectively. Note that the diagnosis of RDD was based on the following definitions: 1) The patient must have had at least two depressive episodes in their life, 2) each episode must have lasted for at least 2 weeks, 3) there must not be enough mood elevation or hyperactivity to be diagnosed as mania, and 4) in women, the episodes must not be directly related to the menstrual cycle. In addition, even if there was elevated mood or hyperactivity, it should be mild.

Here, clinical response in this study was defined as a case in which score improved by 50% or more after an acute course of iTBS treatment from the start of acute iTBS treatment, based on the Montgomery–Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale–17 items (HDRS-17) score. In all cases of iTBS treatment at the clinic, general informed consent for examination and treatment (ie, iTBS) in private practice was given to the patients by the physician in charge. This TMS registry and retrospective observational analysis study was approved by the ITO Yoyogi Mental Clinic Research Ethics Committee (ID: RKK319) and conducted in compliance with the norms and guidelines of the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and the Declaration of Helsinki (revised October 2013) at Shinjuku-Yoyogi Mental Lab Clinic. In accordance with the TMS registry study protocol, informed consent was obtained from the majority of patients, but an opt-out procedure was applied for cases where retrospective consent could not be obtained because of past data. Note that the opt-out procedures refer to the specific disclosure of information regarding the study on the notice board and/or website of the hospital, and if the patient does not wish his or her clinical data to be used in the study, he or she can inform the clinic so that the clinic cannot use the data for research purposes.

Data extraction criteria for this case series

The eligibility criteria for this case series are as follows: (1) 18 years of age or older; (2) patients who met the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and/or International Classification of Diseases, 10th Revision (ICD-10), definitions of the diagnosis of RDD or BD type II with standard psychiatric consultation by certified psychiatrists; (3) patients whose depressive symptoms had not stabilized after a period of standard pharmacotherapy (ie, TRD); (4) patients with no previous history of convulsive seizures; (5) patients with no other apparent contraindications to TMS therapy; and (6) patients who had achieved clinical response or remission with an acute course of iTBS treatment (30 sessions) in the context of TRD. Figure 1 shows a flowchart in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) style.

Clinical measures

The MADRS[32] and HDRS-17[33] scores included in the TMS registry data were used in this case series. In particular, in this study, the MADRS score was used as the primary outcome and the HDRS-17 score as the secondary outcome. The definition of response for both MADRS and HDRS-17 was a decrease by half or less of the pretreatment score with acute iTBS treatment, while the definition of remission was a score ≤ 10 for the MADRS and ≤ 7 for the HDRS-17. In cases where the results for response and remission differed between the two clinical measures, the results from the primary outcome, the MADRS score, were adopted.

Clinical evaluations were performed routinely after every 15 sessions of iTBS treatment by well-trained clinical psychologists. In addition, during the follow-up period after the completion of maintenance iTBS, the MADRS and HDRS-17 assessments were conducted during physician visits at 6-month intervals, as long as the patient could be contacted.

TMS treatment protocol

In the present study, in the context of difficult-to-treatment depression, patients who achieved clinical response to a total of 15–45 sessions of iTBS (double-dose protocol: approximately 6 min with a total of 1200 pulses) as acute treatment were followed by further weekly maintenance iTBS (double-dose protocol: approximately 6 min with a total of 1200 pulses) for a total of 15 sessions (13 patients) or 30 sessions (8 patients) to stabilize the disease and prevent its recurrence. A flow diagram of the acute course of iTBS, maintenance iTBS, and observation period for this case series is shown below (Figure 2).

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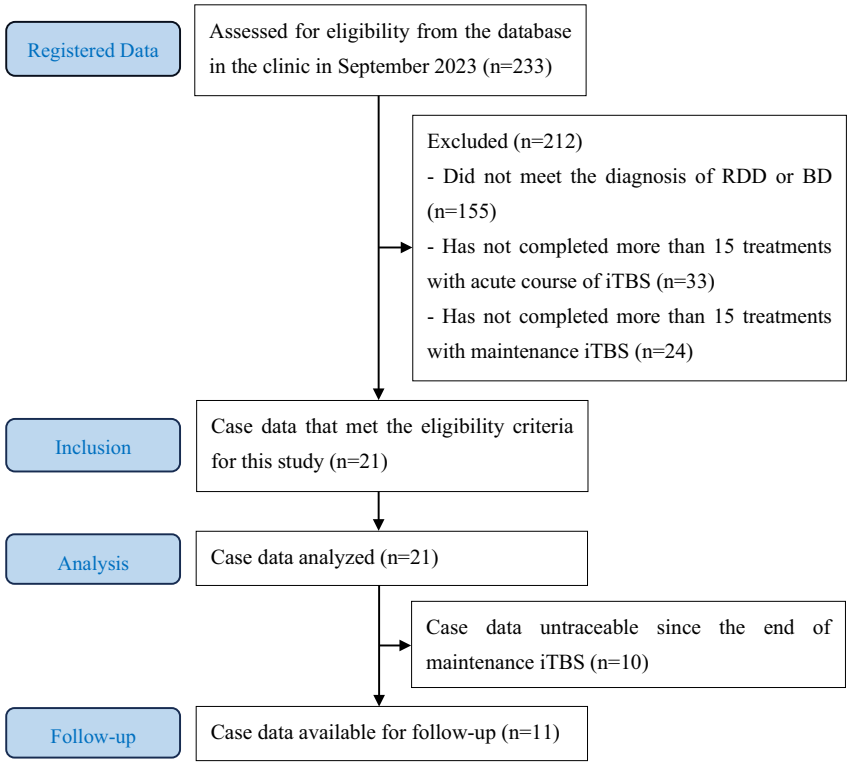

Figure 1. Strengthening the reporting of observational studies in epidemiology (STROBE) flowchart.

Figure 2. A flow diagram of the acute course of iTBS, maintenance iTBS, and observation period for this case series.

In the present iTBS treatment, the left dorsolateral prefrontal cortex (DLPFC) was the target site, including the acute and maintenance phases. The target site on the left DLPFC of each patient was identified using the Beam_F3 method.[34] The resting motor threshold (RMT) was defined as the minimum stimulus intensity to induce muscle contraction in the right abductor pollicis brevis muscle at rest, 50% of the time, with a single pulse of TMS administered to the left primary motor cortex. Stimulation intensity was based on each patient's RMT, with 120% RMT intensity. The MagPro R30 device with the Cool-B70 coil (MagVenture, Inc., Farum, Denmark) was used for the TMS treatment.

Pharmacotherapy during TMS treatment

In principle, there were no medication changes from at least 1 month prior to the introduction of iTBS treatment until the end of acute iTBS treatment except for medication to be used as needed such as anxiolytics and sleep aids. In addition, during the maintenance iTBS period and the follow-up period, most patients were on the same medication in principle, but some patients were reduced or adjusted to the minimum dose of medication necessary based on discussions between the patient and his/her psychiatrist.

Statistical analysis

IBM SPSS Statistics 29 (IBM, Chicago, IL, USA) was used for statistical analysis. The present case series is a preliminary observational study with the main objective of evaluating the effectiveness of maintenance iTBS on a real-world basis. Thus, the primary outcomes of the present study were as follows: 1) for patients who were already in remission on the MADRS or HDRS-17 score at the start of maintenance iTBS, whether they could remain in remission during the maintenance iTBS period and subsequent follow-up period, and 2) for patients who were not in remission but had clinical response to the acute course of iTBS treatment, whether they could keep that response during the maintenance iTBS and follow-up periods. Here, descriptive statistics were provided with respect to these points. In addition, chi-squared test was performed to evaluate whether there were significant differences in maintenance of response or remission up to the last observation, which is the clinical outcome of maintenance iTBS, across diagnoses or sex. The significance level was set at 0.05 in this study.

Results

The clinico-demographic information on the patient data included in this case series is summarized in Table 2, including a breakdown of each item in the RDD and BD groups. In addition, details of the medications the patients were taking during the iTBS treatment period are summarized in Table 3.

The present case series study, which utilized TMS registry data to examine the effects of maintenance iTBS on stabilization of mental condition and prevention of relapse and recurrence in patients who have responded to an acute course of iTBS treatment, yielded the following results. First, the longitudinal changes in the

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Table 2. Clinico-Demographic Information

Characteristics (mean ± S.D.)	All cases	RDD	BD type II	Statistics
Number of individuals; age [years old]	n = 21, 44.6 ± 12.0	n = 10, 44.4 ± 12.2	n = 11, 44.8 ± 12.4	n.s.
Males; age [years old]	n = 13, 43.9 ± 11.7	n = 9, 44.0 ± 12.9	n = 4, 43.8 ± 10.1	n.s.
Females; age [years old]	n = 8, 45.8 ± 13.3	n = 1, –	n = 7, 45.4 ± 14.3	n.s.
Age of onset of an illness [years old]	32.9 ± 12.3	34.9 ± 14.2	31.0 ± 10.6	n.s.
Duration of an illness [years]	11.4 ± 7.4	8.9 ± 7.5	13.6 ± 6.9	n.s.
Number of depressive episodes	4.6 ± 2.0	4.2 ± 2.1	5.0 ± 1.9	n.s.
Duration of current episode [months]	8.0 ± 5.2	10.1 ± 6.7	6.1 ± 2.1	n.s.
MADRS score at the start of maintenance iTBS	9.0 ± 4.2	8.8 ± 3.8	7.4 ± 3.6	n.s.
HDRS–17 score at the start of maintenance iTBS	7.3 ± 3.1	9.3 ± 4.8	7.2 ± 2.7	n.s.
Resting motor threshold (RMT) [%]	45.6 ± 4.7	45.7 ± 4.2	54.9 ± 5.1	n.s.
Stimulus intensity for the left DLPFC (%MSO)	54.8 ± 5.6 (120% RMT)	45.5 ± 5.3	54.6 ± 6.3	n.s.

Abbreviations: BD, bipolar depression; HDRS-17, Hamilton Depression Rating Scale–17 items; iTBS, intermittent theta burst stimulation; MADRS, Montgomery–Åsberg Depression Rating Scale; MSO, maximum stimulator output; n.s., no significant; RDD, recurrent depressive disorder; RMT, resting motor threshold; S.D., standard deviation.

Table 3. Medication Information

Case	Medication
	RDD (n = 10)
1	Olanzapine 10mg, mirtazapine 45mg
2	Lurasidone 20mg, lithium 1400mg, trazodone 50mg
3	Duloxetine 60mg, trazodone 50mg, lemborexant 5mg
4	Venlafaxine 150mg, mirtazapine 45mg, brotizolam 0.25mg
5	Vortioxetine 20mg, loflazepate 1mg
6	Paroxetine 20mg
7	Duloxetine 30mg, zolpidem 10mg
8	Sertraline 100mg, vortioxetine 20mg, trazodone 50mg, quetiapine 50mg, suvorexant 10mg
9	Fluvoxamine 50mg, zolpidem 5mg
10	Sulpiride 150mg, aripiprazole 3mg, zolpidem 5mg
	BD type II (n = 11)
11	Venlafaxine 225mg, lurasidone 20mg, lithium 600mg, quetiapine 12.5mg, suvorexant 20mg
12	Venlafaxine 150mg, lamotrigine 200mg
13	Valproate 800mg, suvorexant 20mg, eszopiclone 3mg
14	Zolpidem 5mg, brotizolam 0.25mg
15	Lamotrigine 200mg, lithium 800mg, lemborexant 10mg
16	Vortioxetine 20mg, valproate 400mg, clonazepam 2mg, lemborexant 5mg
17	Mirtazapine 15mg, lamotrigine 200mg, lithium 600mg, quetiapine 50mg
18	Lithium 600mg, quetiapine 100mg, aripiprazole 6mg
19	Sertraline 25mg, lamotrigine 200mg, valproate 1200mg, eszopiclone 1mg
20	Lamotrigine 400mg, lithium 1200mg, lurasidone 60mg, clonazepam 1mg
21	Perospirone 8mg, suvorexant 10mg

Abbreviations: BD, bipolar depression; RDD, recurrent depressive disorder.

MADRS and HDRS-17 scores with maintenance iTBS in this case series, to the extent that they were followable, are presented in Table 4 below. The MADRS and HDRS-17 scores for each patient are depicted graphically as time series data as Figure 3.

With respect to the MADRS score, for 2 of 21 patients (9.5%), response to acute iTBS treatment, followed by a total of 15 sessions of maintenance iTBS over approximately 4 months, was maintained, but remission was not achieved by the time of the last observation. For the other 19 patients (90.5%), further maintenance iTBS on response or remission after acute iTBS treatment not only maintained response in these patients but also achieved remission, and in all of these cases, remission was maintained until the last observation. Thus, in this case series, a total of 15 to 30 weekly maintenance iTBS sessions after the successful acute iTBS treatment resulted in maintaining the response state for at least 4 months during the maintenance iTBS period and up to 28 months including the follow-up period, according to the assessment at the last observation of the cases that could be followed up.

In addition, chi-squared tests were performed to examine whether differences in diagnosis (RDD or BD type II) or sex (males or females) make a significant contribution to the clinical outcome of maintenance iTBS (ie, maintenance of response or remission). The results showed that, although we did not perform the statistical test for response because all patients maintained response at the time of last observation, no significant difference was found for whether remission was maintained (ie, whether recurrence occurred or not) depending on diagnosis ($\chi^2(1) = 2.43$, $p = 0.214$) or sex ($\chi^2(1) = 1.36$, $p = 0.371$).

The only adverse event during the maintenance iTBS period was mild stimulation site pain (28.6%), and no other serious adverse events, including manic switch or convulsive seizures, were observed. Moreover, our maintenance iTBS was tolerated well and adhered comparatively well due to its minimal side effects and the convenience of only receiving the treatment once a week. Also, there were no changes in prescriptions in the majority of patients during the maintenance period, with the exception of a few

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Table 4. Longitudinal Changes in Scores of the MADRS and HDRS-17 (mean ± S.D.)

Time point	MADRS score	HDRS-17 score
Baseline before acute iTBS (*n* = 21)	24.9 (± 5.3)	14.5 (± 3.6)
Maintenance iTBS Tx0 after the completion of acute iTBS (*n* = 21)	9.0 (± 4.2)	7.3 (± 3.1)
Maintenance iTBS Tx15 (4 months after the completion of acute iTBS) (*n* = 21)	7.0 (± 3.9)	5.8 (± 3.1)
Maintenance iTBS Tx30 (8 months after the completion of acute iTBS) (*n* = 5)[a]	3.8 (± 1.8)	3.6 (± 2.7)
6–month follow–up after the completion of maintenance iTBS (*n* = 11)	4.0 (± 2.3)	3.4 (± 1.9)
12–month follow–up after the completion of maintenance iTBS (*n* = 7)	4.9 (± 1.9)	3.3 (± 1.8)
18–month follow–up after the completion of maintenance iTBS (*n* = 7)	4.3 (± 1.8)	3.4 (± 1.0)
24–month follow–up after the completion of maintenance iTBS (*n* = 5)	3.6 (± 1.5)	2.2 (± 0.4)

[a]Five cases were received 30 sessions of maintenance iTBS.
Abbreviations: HDRS-17, Hamilton Depression Rating Scale–17 items; MADRS, Montgomery–Åsberg Depression Rating Scale.

cases in which the dose of concomitant antidepressants or stabilizers was reduced. In the same period, there were no cases of emergency visits involving self-harm or suicidal behavior. The same was true for adverse events concerning cases that could be followed during the follow-up period after the completion of maintenance iTBS. Moreover, in the BD type II group, no cases of hypomanic/manic episodes, hospitalizations, or suicidal behavior were observed during the follow-up period after the completion of maintenance iTBS.

Discussion

In this case series, 21 patients who had responded to acute iTBS treatment were followed by a total of 15 to 30 sessions of maintenance iTBS, which resulted in sustained response in all patients, with 19 of them also maintaining remission. This case series showed that maintenance iTBS did not worsen depressive symptoms in any case, suggesting that it may contribute to the stabilization of mental condition and the prevention of recurrence. Furthermore, tolerability and safety during the maintenance iTBS period including the follow-up period were also ensured within the observable follow-up range in this case series.

Regarding maintenance rTMS for patients with TRD, the following previous studies have been largely reported.[27, 35] Levkovitz et al. found that in a double-blind sham-controlled RCT of maintenance deep TMS twice a week for 3 months, the active stimulation group (n = 82) maintained a higher percentage of response than the sham stimulation group (n = 77), specifically, immediately after maintenance rTMS response rate for the active group was about 44%, compared to about 26% for the sham group. Regarding the remission rate, the active group had a remission rate of about 32%, while the sham group had a remission rate of only about 22%.[36] Dunner et al. conducted maintenance rTMS in the framework of an observational study and obtained the following results. Patients who achieved response or remission after an acute course of rTMS treatment and then received maintenance rTMS at least once a week for a certain period of time were shown to maintain response (44% and 61%) or remission (29% and 37%) as measured by the Inventory of Depressive Symptom—Self-Report and 9-Item Patient Health Questionnaire, respectively, with a clinical significance over a 12-month follow-up period.[37] In addition, Harel et al. conducted a prospective, open-label study of maintenance deep TMS twice weekly for 8 weeks, followed by once weekly for a total of 10 weeks, and found that improvement in depression with an acute course of rTMS treatment was observed over a follow-up period of approximately 6 months.[38] Richieri et al. also conducted a prospective, open-label study of maintenance rTMS treatment following an acute rTMS treatment tapering regimen. Specifically, a total of 7 sessions of rTMS treatment were administered during the first 3 weeks of the tapering period, followed by weekly rTMS treatment for a total of 2 weeks, then biweekly rTMS treatment for a total of 2 months, and then monthly rTMS treatment for a total of 2 months. The study showed a significantly lower recurrence rate in the maintenance rTMS group (approximately 38%) compared to the non-maintenance rTMS group (approximately 82%). However, the mean time to recurrence was approximately 2.4 months in the maintenance rTMS group versus 2.2 months in the non-maintenance rTMS group, with no significant difference between the two groups.[22] Fitzgerald et al. conducted a prospective, open-label study of clustered maintenance rTMS therapy. Specifically, they administered clustered maintenance rTMS to patients with depression who had responded to two courses of rTMS treatment, with 5 sessions of rTMS treatment over 2 days once a month after the completion of the second course of rTMS treatment. The study, though preliminary, showed that clustered maintenance rTMS may be effective for a subset of patients (non-relapse rate: 29%) after the successful acute course of rTMS treatment.[39] Janicak et al. conducted a multicenter, prospective, open-label, symptom-based maintenance rTMS study. In their study, they administered 5 sessions of rTMS treatment per week for up to a total of 4 weeks, followed by 2 sessions of rTMS treatment for a total of 2 weeks during the 6-month follow-up period after acute rTMS treatment, depending on the depressive symptoms of the patients. As a result, approximately 10% of patients developed recurrence during the 6-month follow-up period. Furthermore, the study showed that the safety and tolerability of maintenance rTMS treatment were similar to those of acute rTMS monotherapy and that the therapeutic effects of maintenance rTMS were also durable, indicating its potential effectiveness as a strategy for preventing the recurrence of depression.[40] Connolly et al. conducted a retrospective cohort study in which maintenance rTMS was administered to 42 patients after the completion of acute rTMS treatment depending on the relapse and recurrence of depressive symptoms. In the study, maintenance rTMS was performed in a tapering manner for a total of 6 months, initially once a week for 4 weeks, then twice a month for 2 months, and then once a month for 3 months. Twenty-six patients (62% of them) remained the response at the time of final evaluation during the maintenance rTMS period. No serious adverse events related to rTMS were observed and well tolerated during the maintenance rTMS period in the study.[41]

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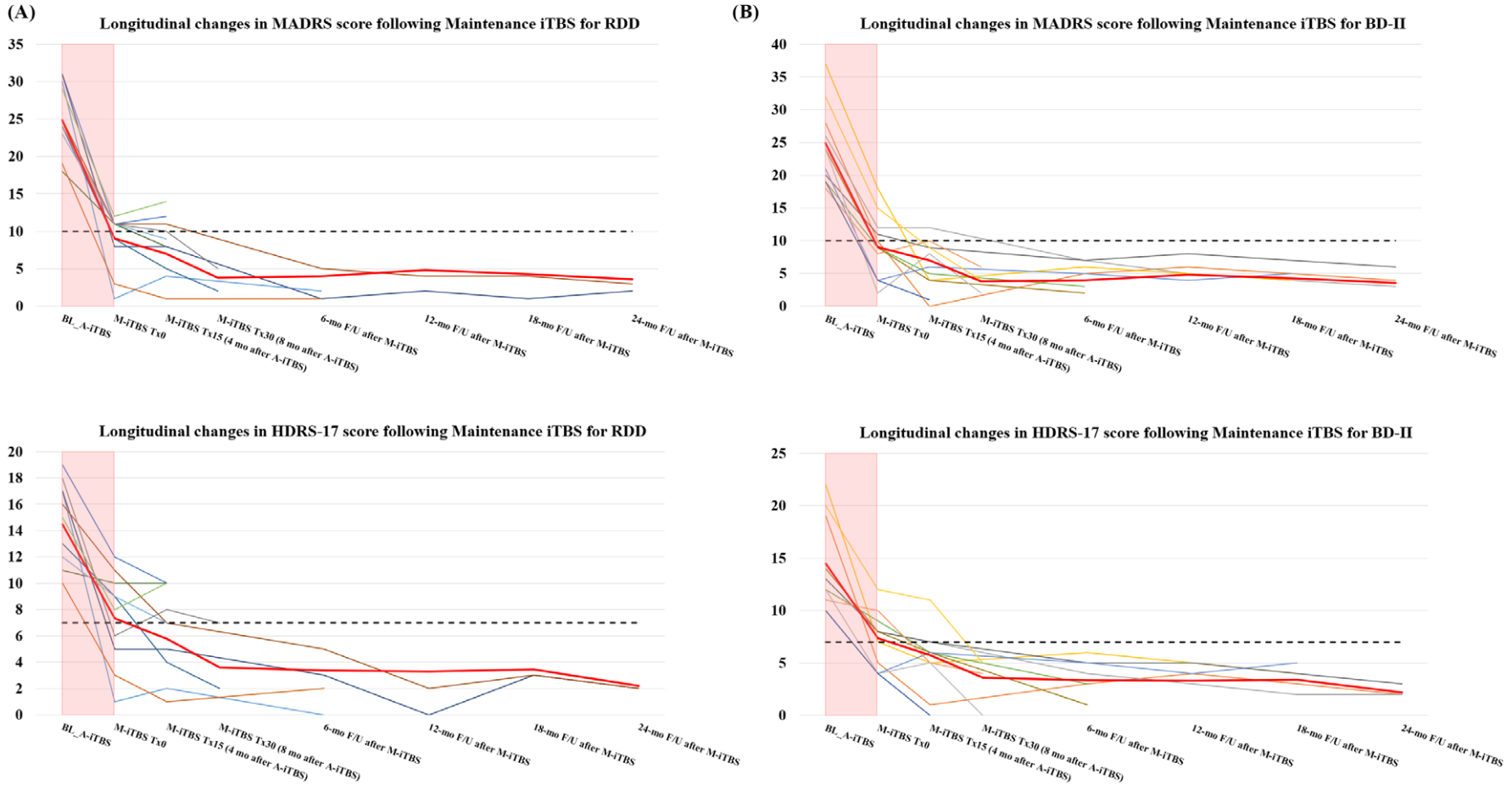

Figure 3. Longitudinal changes in MADRS and HDRS scores in the RDD and BD type II groups from the introduction of maintenance iTBS to the follow-up period. (A) shows the longitudinal changes in MADRS score (upper panel) and HDRS score (lower panel) from the introduction of maintenance iTBS to the follow-up period in the RDD group. (B) depicts the longitudinal changes in MADRS score (upper panel) and HDRS score (lower panel) from the introduction of maintenance iTBS to the follow-up period in the BD type II group. Each color in the line graph indicates a time series change in each patient's score of depressive symptoms. The bold red lines in the figures show the average trajectory of all cases. The black dashed lines in the upper panel show the cutoff lines (10 points) corresponding to remission in the MADRS; similarly, the black dashed lines in the lower panel show the cutoff lines (7 points) for the HDRS-17 score. Of note, the pink bars indicate score changes during the acute iTBS treatment period. A, acute phase; BL, baseline; F/U, follow-up; iTBS, intermittent theta burst stimulation; M, maintenance phase; mo, months.

Taken together, compared to these findings of previous studies, the preventive effect of maintenance rTMS on recurrence in the present case series has maintained a high level of both response and remission, despite the limitations of the study design and sample size. In addition, since a recent observational study by Gama-Chonlon et al. showed that patients with BD may respond better to rTMS than patients with unipolar depression,[42] it is possible that the fact that about half of the cases in this study consisted of patients with BD contributed to the favorable therapeutic as well as preventive effects in this case series. Furthermore, the present maintenance iTBS for the left DLPFC was performed once a week for a total of 15 sessions over a period of approximately 4 months, which is likely to be a promising preventive strategy for relapse and recurrence, in terms of not only its effectiveness but also its feasibility. Furthermore, given the findings of a recent review showing that approximately 54% of patients who were followed up without maintenance treatment after a successful treatment with an acute course of rTMS had recurred at 1 year,[3] the fact that all patients remained the response (ie, none of the cases recurred) during the maintenance iTBS in this case series also indicates that weekly maintenance iTBS is promising.

On the other hand, for the two cases included in this study, the acute course of iTBS treatment did provide the response, but the subsequent maintenance iTBS did not lead to remission (but maintained the response). One had a history of episodic psychotic symptoms associated with BD several months prior to the introduction of acute iTBS treatment, and the severity of the depressive episode was relatively severe at the time of iTBS treatment introduction. The other case had a diagnosis of RDD, but also had a diagnosis of autism spectrum disorder as background pathology, which may have limited the effect of iTBS treatment on the depressive symptoms. Thus, we suspect that the different clinical severity and profile of these two cases compared to the other cases may have prevented maintenance iTBS from having a sufficient stabilizing effect on their symptoms.

In addition, a previous study by Senova and colleagues reported that a higher percentage of female patients and those receiving maintenance therapy had higher response rates at a given time point.[14] Thus, we examined the impact of sex on recurrence rates in this case series but found no significant effect of female sex on the maintenance of remission. The limited sample size of this study allowed only a preliminary examination but verification with a larger sample is awaited in the future. Regarding the impact of maintenance iTBS on retention of response and remission after acute iTBS treatment, we observed its clinically preventive effect on recurrence, despite the limitation that this study was a retrospective, open-label case series. With respect to the impact of different diagnoses of RDD and BD on response and remission with maintenance iTBS, no significant differences were found in the present study. This may be attributed to the background pathology of both diagnoses, which may form a continuum,[43–48] besides the limitation of the small sample size.

Note that the severity of depression in the case series included in this study was for the most part at the mild to moderate level, which was milder than the severity of depression in previous studies. Such differences in clinical background may have contributed to the favorable outcomes of the maintenance iTBS in this study regarding its efficacy in preventing recurrence. More specifically, there are two possible reasons behind this. First, the disparities in clinical practices and depression guidelines between Japan and other countries may contribute to the observed variance in the severity of depression in patients selected for TMS treatment. Secondly, the successful administration of maintenance iTBS over a mid- to long-term period, in terms of preventing relapse and recurrence, may be attributed to the comparatively milder severity of initial depressive episodes relative to prior studies.

The strengths of the present study were as follows. First, we followed up to 28 months with maintenance iTBS after the successful treatment of acute iTBS for a certain number of patients in a real-world clinical setting for the first time. To the best of our knowledge, this case series is the first long-term follow-up observational study beyond 2 years in the world since the few previous studies on maintenance rTMS have usually followed patients for up to 12 months at most. Secondly, in this case series, we focused not on typical cases of TRD, but on more difficult-to-treat depression cases such as RDD and BD, which we believe to be novel. In this sense, this case series is the first challenge of its kind at least in Japan.

One limitation of this study is that, by its nature as an open-label preliminary case series utilizing registry data, it was not an RCT design with a control group, including a sham stimulation condition, and thus, the effect of placebo effect cannot be excluded. However, the placebo effect seems highly unlikely to persist for such a long period of time, since the final observation time point after the completion of acute iTBS treatment in this case series extends to a maximum of 28 months. Next, due to the nature of this report being a case series, the sample size was limited to approximately 20 cases. Therefore, a general conclusion regarding the prevention of relapse and recurrence by maintenance iTBS cannot be drawn from this report by itself, but this study only demonstrated such a possible relapse and recurrence prevention strategy for difficult-to-treat depression. Finally, although we do not have the MADRS and HAMD test data for the patients who responded to acute iTBS treatment but did not receive any maintenance iTBS or who received maintenance iTBS but completed less than 15 sessions because our clinic conducts clinical examinations every 15 sessions, we did not find a single case of clinical worsening of depressive symptoms as a result of receiving maintenance iTBS as far as we could ascertain from the medical records. However, we believe that more detailed follow-up monitoring is needed in the future, to the extent possible, to allow more detailed confirmation of patients' progress and prognosis after the completion of acute iTBS treatment.

In conclusion, despite the above limitations, this case series report suggests that maintenance iTBS for a certain time period after the successful acute iTBS treatment could be a promising strategy that contributes to the stabilization of depressive symptoms and the prevention of mid- to long-term recurrence.[49] Thus, the maintenance iTBS is an approach worth considering more actively not only in Japan but also worldwide in the future. Finally, the findings of this study warrant further investigation in an RCT design with a larger sample size.

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Author contribution. Yoshihiro Noda involved in conceptualization, methodology, investigation, formal analysis, writing the original draft, writing the review and editing, project administration, and supervision. Kyoshiro Fujii involved in investigation and data curation. Shinichiro Nakajima involved in investigation, writing the review and editing. Ryosuke Kitahata involved in investigation and supervision.

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References

1. Rush AJ, Aaronson ST, Demyttenaere K. Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive. *Aust N Z J Psychiatry*. 2019;**53**:109–118.
2. Cowen PJ. Backing into the future: pharmacological approaches to the management of resistant depression. *Psychol Med*. 2017;**47**:2569–2577.
3. Tundo A, De Filippis R, Proietti L. Pharmacologic approaches to treatment resistant depression: evidences and personal experience. *World J Psychiatry*. 2015;**5**:330–341.
4. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr Dis Treat*. 2020;**16**:221–234.
5. Pezawas L, Angst J, Kasper S. Recurrent brief depression revisited. *Int Rev Psychiatry*. 2005;**17**:63–70.
6. Bowden CL, Perlis RH, Thase ME, et al. Aims and results of the NIMH systematic treatment enhancement program for bipolar disorder (STEP-BD). *CNS Neurosci Ther*. 2012;**18**:243–249.
7. Diaz AP, Fernandes BS, Quevedo J, Sanches M, Soares JC. Treatment-resistant bipolar depression: concepts and challenges for novel interventions. *Braz J Psychiatry*. 2022;**44**:178–186.
8. Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;**381**: e073591.
9. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry*. 2003;**60**:261–269.
10. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002; **59**:530–537.
11. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT. Recurrence of major depressive disorder and its predictors in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Psychol Med*. 2013;**43**:39–48.
12. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand*. 2010;**122**:184–191.
13. Vazquez GH, Holtzman JN, Lolich M, Ketter TA, Baldessarini RJ. Recurrence rates in bipolar disorder: systematic comparison of long-term prospective, naturalistic studies versus randomized controlled trials. *Eur Neuropsychopharmacol*. 2015;**25**:1501–1512.
14. Senova S, Cotovio G, Pascual-Leone A, Oliveira-Maia AJ. Durability of antidepressant response to repetitive transcranial magnetic stimulation: systematic review and meta-analysis. *Brain Stimul*. 2019;**12**: 119–128.
15. Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depress Anxiety*. 2004;**20**:98–100.
16. O'reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC Long-term maintenance therapy for major depressive disorder with rTMS. *J Clin Psychiatry*. 2005;**66**:1524–1528.
17. Langguth B, Landgrebe M, Zowe M, Gerst M, Hajak G, Eichhammer P. Repetitive transcranial magnetic stimulation for maintenance treatment of depression: a case report. *J Clin Psychiatry*. 2006;**67**:835–836.
18. Fitzgerald PB, Benitez J, De Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. *Aust N Z J Psychiatry*. 2006;**40**:764–768.
19. Chatterjee B, Kumar N, Jha S. Role of repetitive transcranial magnetic stimulation in maintenance treatment of resistant depression. *Indian J Psychol Med*. 2012;**34**:286–289.
20. Cristancho MA, Helmer A, Connolly R, Cristancho P, O'reardon JP. Transcranial magnetic stimulation maintenance as a substitute for maintenance electroconvulsive therapy: a case series. *J ECT*. 2013;**29**:106–108.
21. Noda Y, Daskalakis ZJ, Ramos C, Blumberger DM. Repetitive transcranial magnetic stimulation to maintain treatment response to electroconvulsive therapy in depression: a case series. *Front Psychiatry*. 2013;**4**:73.
22. Richieri R, Guedj E, Michel P, et al. Maintenance transcranial magnetic stimulation reduces depression relapse: a propensity-adjusted analysis. *J Affect Disord*. 2013;**151**:129–135.
23. Kelly MS, Oliveira-Maia AJ, Bernstein M, et al. Initial response to transcranial magnetic stimulation treatment for depression predicts subsequent response. *J Neuropsychiatry Clin Neurosci*. 2017;**29**:179–182.
24. Pridmore S, Erger S, Rybak M, Kelly e, may t. Early relapse (ER) transcranial magnetic stimulation (TMS) in treatment resistant major depression. *Brain Stimul*. 2018;**11**:1098–1102.
25. Matsuda Y, Yamazaki R, Shigeta M, Kito S. A 12-month maintenance therapy using repetitive transcranial magnetic stimulation for treatment-resistant depression: a report of two cases. *Asian J Psychiatry*. 2022;**68**:102970.
26. Cosmo C, Zandvakili A, Petrosino NJ, Berlow YA, Philip NS. Repetitive transcranial magnetic stimulation for treatment-resistant depression: recent critical advances in patient care. *Curr Treat Options Psychiatry*. 2021;**8**:47–63.
27. 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.
28. D'andrea G, Mancusi G, Santovito MC, et al. Investigating the role of maintenance TMS protocols for major depression: systematic review and future perspectives for personalized interventions. *J Pers Med*. 2023;**13**:697.
29. Fukuda AM, Tirrell E, Gobin AP, Carpenter LL. Repetitive transcranial magnetic stimulation for depression relapse or recurrence: naturalistic retreatment series outcomes. *Brain Stimul*. 2019;**12**:1328–1329.
30. Noda Y, Kizaki J, Takahashi S, Mimura M. TMS Database Registry Consortium Research Project in Japan (TReC-J) for future personalized psychiatry. *J Pers Med*. 2022;**12**:844.
31. Ekman CJ, Popiolek K, Boden R, Nordenskjold A, Lundberg J. Outcome of transcranial magnetic intermittent theta-burst stimulation in the treatment of depression - a Swedish register-based study. *J Affect Disord*. 2023;**329**:50–54.
32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;**134**:382–389.
33. Hamilton M. Rating depressive patients. *J Clin Psychiatry*. 1980;**41**:21–24.
34. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul*. 2009;**2**:50–54.
35. Chang J, Chu Y, Ren Y, Li C, Wang Y, Chu XP. Maintenance treatment of transcranial magnetic stimulation (TMS) for treatment-resistant depression patients responding to acute TMS treatment. *Int J Physiol Pathophysiol Pharmacol*. 2020;**12**:128–133.
36. Levkovitz Y, Isserles M, Padberg F, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*. 2015;**14**:64–73.
37. Dunner DL, Aaronson ST, Sackeim HA, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *J Clin Psychiatry*. 2014;**75**:1394–1401.
38. Harel EV, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: an 18-week continuation safety and feasibility study. *World J Biol Psychiatry*. 2014;**15**:298–306.
39. Fitzgerald PB, Grace N, Hoy KE, Bailey M, Daskalakis ZJ. An open label trial of clustered maintenance rTMS for patients with refractory depression. *Brain Stimul*. 2013;**6**:292–297.
40. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimul*. 2010;**3**:187–199.
41. Connolly KR, Helmer A, Cristancho MA, Cristancho P, O'reardon JP. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *J Clin Psychiatry*. 2012;**73**:e567–e573.
42. Gama-Chonlon L, Scanlan JM, Allen RM. Could bipolar depressed patients respond better to rTMS than unipolar depressed patients? A naturalistic, observational study. *Psychiatry Res*. 2022;**312**:114545.
43. Bukh JD, Andersen PK, Kessing LV Rates and predictors of remission, recurrence and conversion to bipolar disorder after the first lifetime episode of depression--a prospective 5-year follow-up study. *Psychol Med*. 2016;**46**: 1151–1161.

https://doi.org/10.1017/S109285292400035X Published online by Cambridge University Press

44. Gilman SE, Dupuy JM, Perlis RH Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2012;**73**:829–836.
45. Holma KM, Melartin TK, Holma IA, Isometsa ET Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. *J Clin Psychiatry*. 2008;**69**:1267–1275.
46. Jo YT, Joo SW, Kim H, et al. Diagnostic conversion from unipolar to bipolar affective disorder-a population-based study. *J Affect Disord*. 2022;**301**: 448–453.
47. Nestsiarovich A, Reps JM, Matheny ME, et al. Predictors of diagnostic transition from major depressive disorder to bipolar disorder: a retrospective observational network study. *Transl Psychiatry*. 2021;**11**:642.
48. Tse AC, Fok ML, Yim LC, Leung MM, Leung CM. Diagnostic conversion to bipolar disorder in unipolar depressed patients in Hong Kong: a 20-year follow-up study. *J Affect Disord*. 2021;**286**:94–98.
49. Elsayed OH, Ercis M, Pahwa M, Singh B. Treatment-resistant bipolar depression: therapeutic trends, challenges and future directions. *Neuropsychiatr Dis Treat*. 2022;**18**:2927–2943.

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