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Accelerated repetitive Transcranial Magnetic Stimulation (aTMS) vs. standard repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of Major Depressive Episodes: A randomized, single-blind, controlled trial

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ABSTRACT

Introduction: Repetitive Transcranial Magnetic Stimulation (rTMS) has demonstrated both safety and efficacy in the treatment of Depressive Episodes but requires daily treatment over 4–6 weeks. Accelerated TMS (aTMS), which delivers all treatments within a few days, offers potential advantages in improving accessibility and enhancing patient adherence.

Methods: In order to evaluate the effectiveness of aTMS compared to regular daily rTMS, 33 inpatients affected by Major Depressive Episodes treated with either Fluvoxamine or Venlafaxine were enrolled. Patients were randomly assigned to the two protocol groups: standard rTMS group (15 patients) and aTMS group (18 patients). In the standard protocol, patients received 1 rTMS session/day for 4 weeks, while in the aTMS protocol they received 4 rTMS sessions/day for 5 days. Symptomatological improvement was evaluated through MADRS, BDI-II and SSI rating scales. The study was single-blind. Response and remission rates were calculated, defined respectively as a reduction $\geq$ 50 % in the MADRS score and a MADRS score $<$ 10.

Results: The analysis was carried out on 31 patients (18 in the aTMS group and 13 in the rTMS group). The aTMS and rTMS response rates were respectively 72 % vs. 38.5 % on day 28 ($p = 0.040$) and 83.3 % vs. 38.5 % on day 56 ($p = 0.011$). The aTMS and rTMS group remission rates were respectively 67 % vs. 15.4 % on day 28 ($p = 0.0001$) and 61 % vs. 30,8 % on day 56 ($p = 0.006$). Concerning side effects, no statistically significant differences were observed between the two groups.

Conclusions: Treatment with aTMS seems faster and more effective than treatment with standard rTMS in improving the clinical condition in patients with Major Depressive Episodes, allowing to treat patients in just 5 days instead of 4 weeks, without impacting on side effects and tolerability.

1. Introduction

Major Depressive Disorder (MDD) is a frequent and disabling condition (WHO, Depression and Other Common Mental Disorders Global Health Estimates (World Health Organization), 2017). Despite the variety of pharmacological options, many patients experience suboptimal responses or eventual relapse, leading to the concept of treatment-resistant depression (TRD). Typically, failure to respond to at least two adequate trials of antidepressants (often SSRIs, SNRIs, or TCAs) is used to characterize TRD, although definitions can vary (Papakostas, 2009; Rush et al., 2006). In the search for newer and more effective treatments, in the last decades repetitive Transcranial Magnetic

Abbreviations: TMS, Transcranial Magnetic Stimulation; aTMS, accelerated Transcranial Magnetic Stimulation, MADRS, Montgomery Asberg Depression Rating Scale; BDI-II, Beck Depression Inventory II; SSI, Scale of Suicidal Ideation; l-DLPFC, left dorsolateral prefrontal cortex; MDD, Major Depressive Disorder; TRD, Treatment-Resistant Depression; iTBS, intermittent theta-burst stimulation.

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Stimulation (rTMS) has repeatedly shown an antidepressant effect. The FDA approved the first rTMS treatment protocol in 2008 (Perera et al., 2016), based on the results of a randomized, sham-controlled multicentre clinical trial by O'Reardon et al. (2007), which demonstrated TMS superiority over placebo over the left dorsolateral prefrontal cortex (l-DLPFC) (Lefaucheur et al., 2014). Common parameters investigated in this trial were 120 % of motor threshold (MT), 10 Hz frequency, train duration of 4 s, inter-train interval (ITI) of 26 s and 75 trains (3000 pulses) per session over 37.5 min for 4 weeks (5 sessions/week). In order to reduce the length of each session, the ITI was subsequently shortened to 11 s without affecting overall efficacy, thereby bringing session duration to 19 min. To date, the clinical evidence of the antidepressant effect of rTMS, either alone or in combination with antidepressant or psychotropic medications, is highly consistent, with over 15 meta-analyses and a large number of systematic reviews strongly supporting its use in MDD (Perera et al., 2016).

Despite the effectiveness of rTMS, several limitations emerged soon, advocating the need to optimize the protocols. Even if significantly superior to sham treatments, the response and remission rates with standard protocols are still relatively modest, around 30 % and 20 % (Berlim et al., 2014). However, more recent trials, such as the Three-D study (Blumberger et al., 2018), have shown higher response and remission rates (up to around 49 % and 32 %, respectively), reflecting ongoing refinements in TMS parameters and patient selection. Additionally, the duration of the whole treatment can be 4–6 weeks, sometimes even longer (Perera et al., 2016), which may be less feasible for patients with acute and severe symptoms (e.g., suicidal ideation) who might benefit from rapid resolution of depression. To improve these outcomes, different strategies have been implemented, including the individualization of rTMS parameters and the use of accelerated protocols (Baeken, 2018).

The accelerated rTMS (aTMS) is an intensified approach in which multiple daily sessions are applied in order to reduce the total length of the treatment from several weeks to a few days, though protocols vary widely: some deliver the same total number of pulses (Baeken, 2018), while others (e.g., SAINT or SNT protocols) administer significantly more pulses per day (Cole et al., 2020; van Rooij et al., 2024). Holtzheimer et al. (2010) were the first to introduce an accelerated treatment as beneficial to the patient in a very limited time, through a two-day-long open-label trial (5 sessions on day 1 and 10 sessions on day 2) with a total of 15,000 pulses, showing a significant treatment effect at day 3, sustained until week 6. Interestingly, no safety concerns arose from this trial, even though the total number of pulses was lower than the FDA-approved standard protocol. Since then, a few more trials have been conducted, both open-label and RCTs. Baeken et al. (2013) and George et al. (2014) both compared aTMS with sham TMS, identifying a rapid antidepressant effect (Baeken et al., 2013) and antisuicidal effect (George et al., 2014). Fitzgerald et al. (2018) instead compared aTMS with standard rTMS treatment, with no significant difference in terms of response and relapse rates. In all these trials, no serious safety concerns emerged, thus supporting the tolerability of accelerated protocols (Fitzgerald et al., 2018; George et al., 2014).

Nonetheless, there remains a lack of consensus regarding optimal aTMS parameters, given the small number of patients included in most studies, the variability in patient selection (e.g., unipolar vs. bipolar depression), and the different ways total pulses can be "accelerated." As highlighted in the review by van Rooij et al. (2024), only a few protocols exist, and they diverge across key elements such as treatment frequency, cumulative exposure, individualized parameters, and brain state.

The aim of this study is to compare aTMS with a standard treatment protocol using one of the FDA-approved parameter sets (i.e., 10 Hz, 120 % MT, total of 60,000 pulses). Although many clinical settings now extend rTMS to six weeks (30 sessions), we opted for a four-week, 20-session protocol to match our accelerated arm's total pulse count and maintain methodological consistency with several foundational rTMS trials (O'Reardon et al., 2007). The main hypothesis is to investigate whether an intensive approach might maintain comparable or enhanced response rates, but in a shorter time interval (1 week vs. 4 weeks), thus potentially improving treatment adherence, accessibility, and the rapidity of symptom relief.

2. Methods

2.1. Study design

The study is a national, single-center, comparative, parallel, two-arm, single-blind randomized controlled trial, with participants randomized to either accelerated TMS (aTMS) or standard rTMS using a computer-generated randomization list. The rater who assessed the evaluation scales was blinded to the assigned treatment protocol, and patients were instructed not to reveal which protocol they received. The blind rater had no access to the patients' clinical history and other clinical information. The study was approved by the Ethics Committee of IRCCS San Raffaele Hospital (approval number 170/INT/2019, approved on November 7, 2019). All participants provided written informed consent prior to enrollment.

2.2. Participants

Patients were recruited from the inpatient Mood Disorder Unit at the San Raffaele Turro Hospital in Milan. They had to have a Major Depressive Episode (MDE), either unipolar or bipolar, with moderate to severe depression, defined by a Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) score of $>$ 19. We included both Major Depressive Disorder (MDD) and Bipolar Disorder (BD), given that rTMS has shown promising results in bipolar depression as well (Dell'Osso et al., 2009; Nguyen et al., 2021). Additional inclusion criteria were nonresponse to at least one antidepressant (SSRI, SNRI, or TCA) during the current episode, age 18–70, and a baseline Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score $>$ 25. Patients were excluded if they had any contraindication to TMS (Hardy et al., 2016) – such as cardiac pacemakers, metal implants in the head, cochlear implants, microinfusion pumps, or other implanted electronic devices – a history of epilepsy, major neurological disorders, neurosurgeries, clinically unstable medical illnesses, active psychotic symptoms, personality disorders, neurodegenerative disorders, alcohol or substance abuse in the last 6 months, or pregnancy.

Over an 18-month recruitment period, we screened 100 inpatients admitted to the Mood Disorder Unit at San Raffaele Turro Hospital in Milan. A total of 67 patients were excluded, primarily because they did not meet the pharmacological inclusion criteria. Specifically, many were not being treated with either Venlafaxine or Fluvoxamine, while others were taking medications not permitted by the protocol (e.g., antiepileptic drugs), thus meeting exclusion criteria. These pharmacological restrictions were adopted in order to maintain a more homogeneous treatment background across participants and to avoid potential interference with TMS safety and efficacy. Additional exclusions were due to other standard clinical contraindications (e.g., epilepsy, implanted devices, or unstable medical conditions) or patient refusal to participate. Ultimately 33 patients met all criteria and were enrolled: 15 were randomized to the standard rTMS arm and 18 to the aTMS arm. A slight imbalance (15 vs. 18) resulted from the computer-generated sequence. Among these 33, 2 participants in the standard rTMS group withdrew early (one before starting due to a new pharmacological therapy conflicting with inclusion criteria, another during treatment due to discomfort), resulting in 31 patients included in the final analyses. Of these, 22 had Major Depressive Disorder (MDD) and 9 had Bipolar Disorder (BD). Specifically, the aTMS group comprised 12 patients with MDD and 6 with BD, while the standard rTMS group included 10 patients with MDD and 3 with BD. All BD patients received mood stabilizer treatment throughout the study. Additionally, all participants remained hospitalized as inpatients for the full duration of their assigned TMS

protocol, allowing for consistent monitoring, protocol adherence, and accurate clinical assessments.

2.3. Medication and concomitant treatments

Both the aTMS and standard rTMS groups received either Fluvoxamine or Venlafaxine, in order to maintain a more homogeneous pharmacological profile. Although our protocol allowed for a minimum of 2 weeks on a stable dosage based on prior TMS trials (George et al., 2000), subsequent review of patient records showed that all participants had actually been on a stable antidepressant dose for 4–6 weeks before TMS initiation, in line with consensus guidelines indicating that 4–6 weeks of stability may further minimize variability (Hiemke et al., 2018). Additional allowed treatments included lithium, hypnotic benzodiazepines, hypnotic non-benzodiazepines, short half-life benzodiazepines, antipsychotics, and other non-psychotropic therapies. Anti-epileptic drugs (e.g., pregabalin, gabapentin, valproate, carbamazepine, lamotrigine, topiramate, oxcarbazepine) were excluded because they may alter seizure threshold or interfere with TMS efficacy (Hardy et al., 2016). If a patient was taking a non-allowed medication, it was discontinued for at least five half-lives before TMS. Five half-lives is the time needed to reduce the plasma level of the drug to a negligible level (Hiemke et al., 2018).

2.4. Clinical measures

Demographic variables were recorded at baseline following a clinical interview. To investigate clinical effects, the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) was assessed at baseline, day 1, day 2, day 3, day 4, day 5, and at the end of weeks 2, 3, 4, and 8. Patients were also assessed at the same time points with the Beck Depression Inventory II (BDI-II) (Beck et al., 1996). The Scale of Suicidal Ideation (SSI) (Beck et al., 1979) was administered at baseline, day 1, day 5, and at the end of weeks 2, 3, 4, and 8. Response was defined as a reduction $\geq$ 50 % of the MADRS score compared to baseline, while remission was defined as a MADRS score < 10 (Hawley et al., 2002). Cognitive tests were conducted at baseline with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975).

2.5. TMS treatment

Patients received one of two treatment schedules:

- Accelerated rTMS (aTMS) treatment protocol: patients received 4 rTMS sessions per day for 5 days. In each session, 75 trains of 10 Hz rTMS were applied to the left DLPFC, at 120 % of the resting motor threshold. The train duration was 4 s, with an Inter Train Interval (ITI) of 11–26 s according to tolerability. In total, each participant underwent 20 sessions, with a total of 60,000 pulses. Each session was followed by at least 1 h of rest. We chose 4 daily sessions based on prior accelerated protocols (George et al., 2014; Holtzheimer et al., 2010), balancing feasibility and tolerability.
- Standard rTMS treatment protocol: One session per day for 5 days per week over 4 weeks. In each session, the same parameters were used (75 trains of 10 Hz rTMS at 120 % MT, 4-second trains, ITI 11–26 s), for a total of 20 sessions and 60,000 pulses. A 4-week schedule was selected to match the total sessions and pulses in the aTMS arm and to maintain consistency with prior rTMS trials (Lefaucheur et al., 2014; O'Reardon et al., 2007).

Before initiating TMS, the resting motor threshold (MT) was determined using the TMS device in single-pulse mode (Farzan, 2014; Fitzgerald & Daskalakis, 2022). rTMS was delivered using a Magstim Rapid2 with a 70 mm Air Cooled Double Coil.

2.6. Study objectives

The primary objective was to evaluate the rapidity of antidepressant efficacy of aTMS compared to standard rTMS within 4 weeks, measured by changes in Montgomery-Åsberg Depression Rating Scale (MADRS) scores. The secondary objectives included comparing the overall antidepressant effect at week 8 (MADRS), the patients' subjective antidepressant effect at week 8 (BDI-II), and the anti-suicidal effect at week 8 (SSI). Additionally, an exploratory subgroup analysis was performed to compare outcomes in MDD vs. BD, given that both diagnoses were included in our sample.

2.7. Data analysis

We performed t-tests, χ^2 tests, Fisher exact tests, or Mann-Whitney tests to examine between-group differences in baseline demographic and clinical variables. The primary endpoint (MADRS reduction) was analyzed using ANOVA for repeated measures. For secondary endpoints (BDI-II, SSI), mixed-model ANCOVA was applied, using baseline scores as covariates. Participants who discontinued early ($n = 2$) were excluded from the final analysis. Statistical significance was set at $p < 0.05$, two-tailed. Analyses were conducted using SPSS version 22.0 (IBM Corp, 2013).

3. Results

As shown in Table 1, the two treatment groups were comparable for sex, age, age of onset, diagnosis, current episode duration, number of episodes, preceding normothymia duration, family history, and pharmacological therapy.

Of the initial 100 inpatients screened, 33 met inclusion criteria and were enrolled, with 18 randomized to aTMS and 15 to standard rTMS. Two participants in the standard arm withdrew early, leaving 31 patients (18 aTMS, 13 standard) in the final analysis. Further details are illustrated in the CONSORT flowchart (Fig. 1).

All patients started with moderate-to-severe depression according to MADRS and BDI-II scores. A detailed summary of the mean scores and standard deviations for both MADRS and BDI-II, at each time point

Table 1
A = χ^2 test, b = Mann-Whitney test, c = T-test, d = Fisher's exact test.

Characteristic	aTMS (N = 18)	rTMS (N = 13)	*p*-value
Sex (M/F)	7/11	5/8	0.682[a] (χ^2 = 0.17)
Age (years, median, IQR)	56 (52–60)	59 (54–63)	0.731[b] (U = 109.5)
Age of onset (years, mean ± SD)	36.5 ± 12.8	34.3 ± 13.5	0.612[c] (t = 0.51)
Diagnosis (MDD/BD)	12/6	10/3	0.432[a] (Fischer = 0.62)
Current episode duration (months, mean ± SD)	7.5 ± 5.6	6.2 ± 4.5	0.658[c] (t = 0.44)
n° episodes (median, IQR)	5.8 (4.6–5.9)	4.5 (4.2–6.3)	0.571[b] (U = 106.0)
Preceding normothymia duration (months, median, IQR)	23 (8–46)	18 (10–30)	0.592[b] (U = 112.0)
Familiarity (yes/no)	11/7	6/7	0.379[a] (χ^2 = 0.78)
Antidepressant (Fluvoxamine/Venlafaxine)	10/8	8/5	0.421[a] (χ^2 = 0.65)
Lithium (yes/no)	5/13	4/9	0.543[a] (Fisher = 0.58)
Antipsychotics (yes/no)	9/9	7/6	0.647[a] (Fisher = 0.70)
Benzodiazepines (yes/no)	16/2	11/2	0.583[a] (Fisher = 0.54)

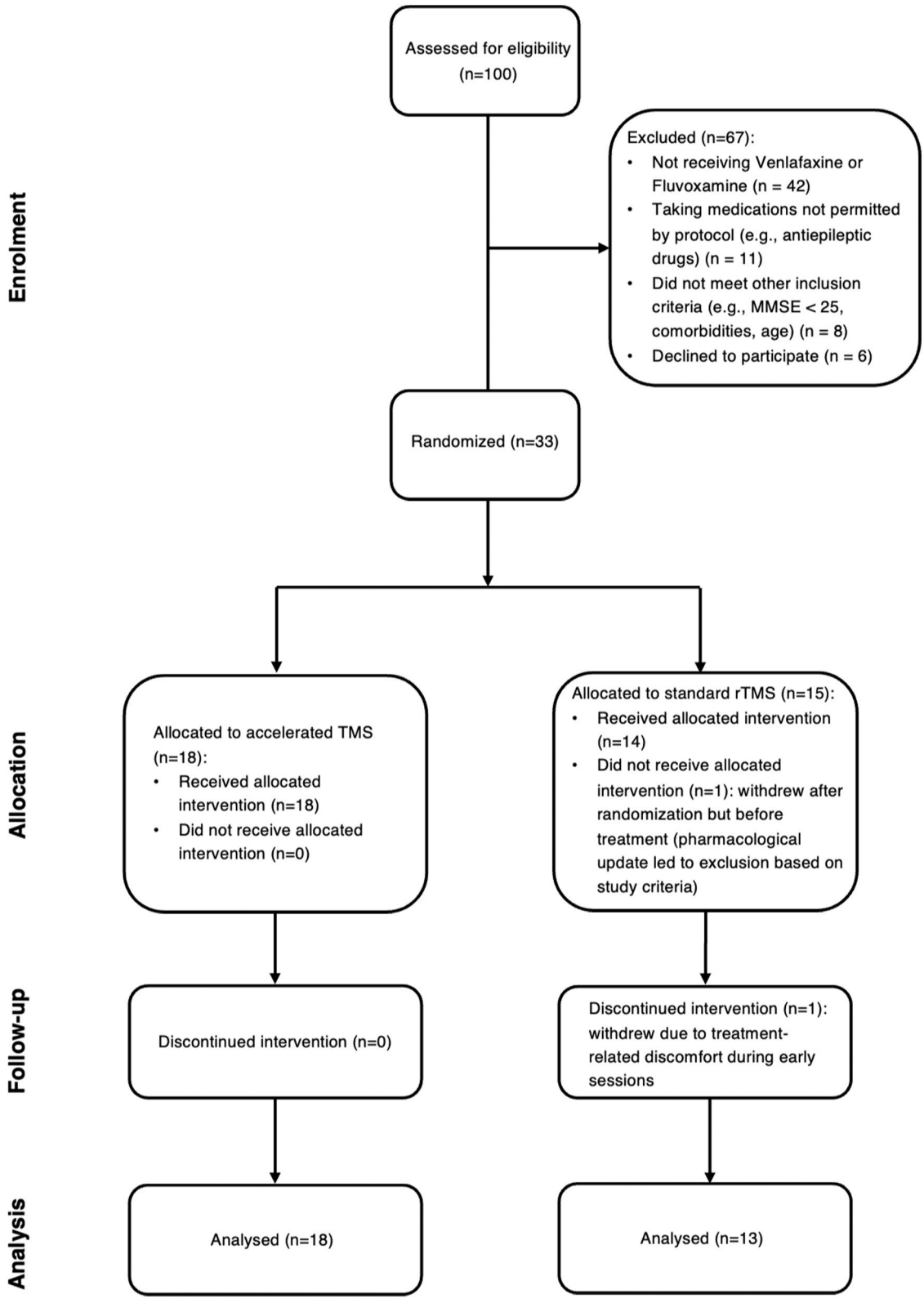


Fig. 1. CONSORT diagram for study.

across the study period for both treatment groups, is provided in Table 2.

Fig. 2 shows the comparison between the MADRS mean scores in the two protocol groups. At baseline, the aTMS group had a statistically higher MADRS mean than the standard rTMS group ($p = 0.028$). Fig. 3 shows the comparison of BDI-II mean scores, also indicating a higher baseline in the aTMS group ($p = 0.037$). Both figures illustrate a sharper initial score reduction in the aTMS group, particularly during the first five days.

Analyzing the trend of MADRS and BDI-II from day 0 to day 56, the difference between the two protocols remained significant. A faster decline occurred in the first 5 days ($p = 0.001$ for MADRS; $p = 0.048$ for BDI-II). Moreover, at day 56, aTMS patients still exhibited lower MADRS

Table 2
Mean (± SD) MADRS and BDI-II scores for aTMS and rTMS groups at each assessment time point.

Timepoint	MADRS aTMS (Mean ± SD)	MADRS rTMS (Mean ± SD)	BDI-II aTMS (Mean ± SD)	BDI-II rTMS (Mean ± SD)
Day 0	30.1 ± 4.6	25.1 ± 4.8	32.2 ± 6.4	28.1 ± 6.5
Day 1	26.5 ± 4.5	24.0 ± 4.4	31.0 ± 6.2	29.2 ± 6.2
Day 2	23.7 ± 4.4	24.5 ± 4.6	28.5 ± 5.8	29.0 ± 6.0
Day 3	20.0 ± 5.8	23.2 ± 5.6	26.8 ± 7.1	30.0 ± 7.3
Day 4	17.8 ± 4.7	22.3 ± 4.8	26.0 ± 6.7	29.0 ± 6.9
Day 5	16.2 ± 5.2	21.1 ± 5.0	25.1 ± 7.2	28.1 ± 7.5
Day 14	14.5 ± 5.3	20.2 ± 5.6	20.2 ± 6.0	24.0 ± 7.1
Day 21	13.8 ± 5.1	19.8 ± 5.8	17.7 ± 7.1	23.0 ± 6.6
Day 28	12.4 ± 5.7	17.7 ± 6.0	17.2 ± 6.8	23.9 ± 6.7
Day 56	11.0 ± 5.4	16.6 ± 6.1	14.0 ± 6.5	24.2 ± 7.4

and BDI-II scores compared to the standard rTMS arm ($p = 0.001$ for MADRS and $p = 0.032$ for BDI-II). This suggests an overall superior effect of the accelerated protocol in ameliorating depressive symptoms. Focusing on just the first 5 days, in which aTMS was actively administered, there was a notably larger drop in MADRS and BDI-II compared to standard rTMS ($p = 0.001$ and $p = 0.032$, respectively). Regarding suicidal risk, assessed via the SSI scale, no significant differences emerged ($p = 0.621$).

We performed a matched comparison of clinical outcomes after each group completed 20 sessions: Day 5 for aTMS vs. Day 28 for standard rTMS (Fig. 4). The aTMS group's mean MADRS on Day 5 was 16.2 ± 5.2, whereas the rTMS group's mean MADRS on Day 28 was 17.7 ± 6.0 ($p = 0.043$), signifying a statistically significant aTMS advantage. By contrast, for the BDI-II at those respective times, 25.2 ± 7.2 vs. 23.9 ± 6.7, the difference did not reach significance ($p = 0.24$).

An exploratory subgroup analysis dissecting MDD vs. BD at all assessment points (MADRS and BDI-II) revealed no statistical disparities in improvement trajectories ($p = 0.42$), suggesting that both unipolar and bipolar patients may benefit similarly.

In terms of response, defined as a reduction of the MADRS score ≥ 50 % compared to baseline, the accelerated group displayed higher rates at Day 28 (72 % vs. 38.5 %, $p = 0.040$) and Day 56 (83.3 % vs. 38.5 %, $p = 0.011$). For remission, defined as a MADRS score < 10 points, the aTMS protocol also outperformed standard rTMS at both Day 28 (67 % vs. 15.4 %, $p = 0.0001$) and Day 56 (61 % vs. 30.8 %, $p = 0.006$).

Concerning the safety, despite providing a high dose of daily treatment (300 trains of stimulation per day over 4 sessions in the aTMS group vs. 75 trains over 1 session in the standard rTMS group), accelerated treatment was not associated with any serious adverse event and the analysis did not show a statistically significant impact regarding side effects, which were however mild in both groups, including site discomfort (46.2 % in aTMS vs. 36.4 % in standard rTMS, $p = 0.484$), headache (38.5 % in aTMS vs. 27.3 % in standard rTMS, $p = 0.696$), and sleep alterations (5.56 % in aTMS vs. 0 % in standard rTMS, $p = 1.000$). Therefore, the accelerated protocol does not seem to adversely influence the side effects and is equally safe and tolerable compared to the standard protocol currently in use.

4. Discussion

Our study, consistent with previous findings (Baeken, 2018; Holtzheimer et al., 2010; van Rooij et al., 2024), demonstrated that accelerated TMS is a safe and effective treatment for Major Depressive Episodes. Prior research has consistently highlighted the safety and efficacy of aTMS in improving depressive symptoms, particularly in treatment-resistant populations. For example, Holtzheimer et al. conducted an early exploration of aTMS for treatment-resistant depression and noted its non-inferiority compared to standard repetitive TMS (rTMS), highlighting a potentially more rapid symptom response (Holtzheimer et al., 2010). Similarly, Baeken et al. reviewed the evidence supporting aTMS as a viable alternative to standard rTMS, particularly for patients with refractory depression (Baeken, 2018).

Building on this foundation, our findings suggest a potential superiority of aTMS over the standard protocol in terms of speed of clinical improvement. In particular, we observed faster and more pronounced reductions in depressive symptoms with the accelerated regimen during the first 5 days, when the aTMS group completed 20 sessions. Even when matching the total "dose" of treatment - 20 sessions at day 5 for aTMS vs. day 28 for standard rTMS - MADRS scores continued to show a statistically significant advantage for aTMS. This aligns with findings from

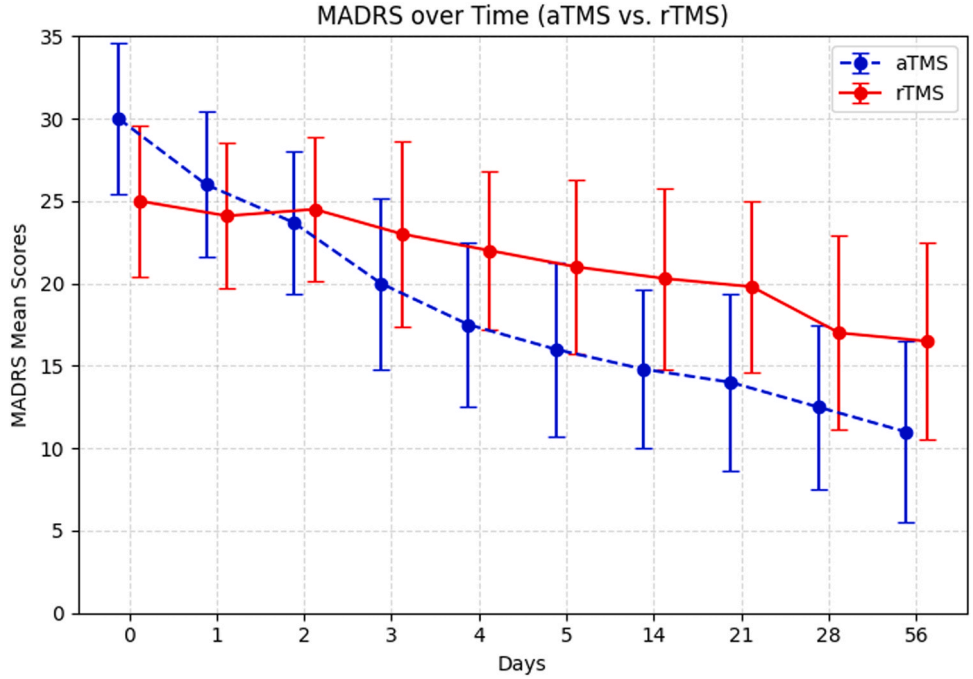


Fig. 2. MADRS mean scores in aTMS and rTMS protocols from baseline to week 8 (End of Study).

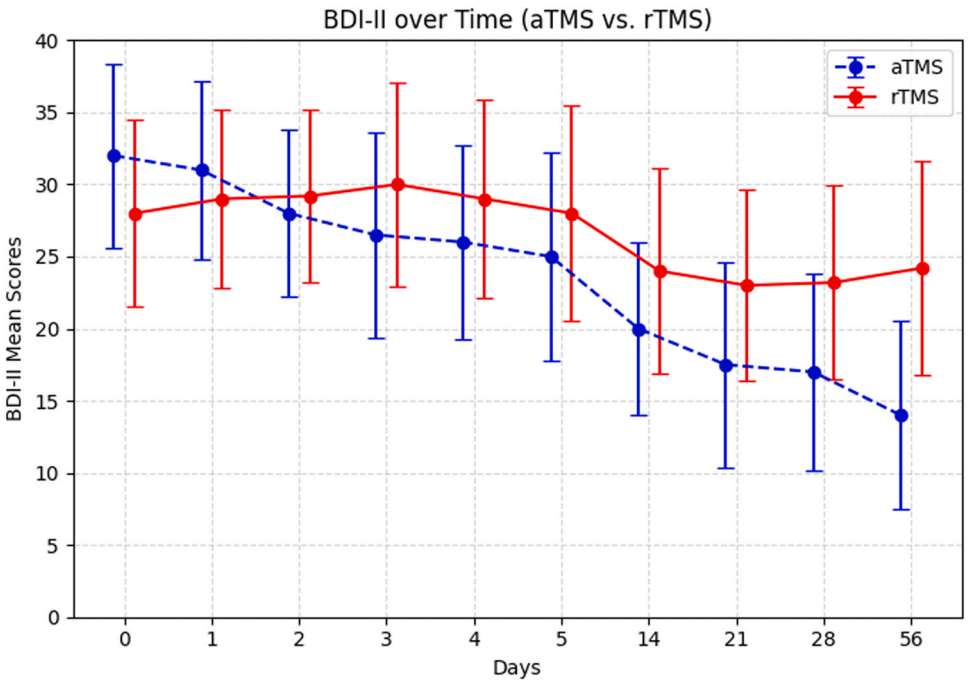


Fig. 3. BDI-II mean scores in aTMS and rTMS protocols from day 0 to day 56 (End of Study).

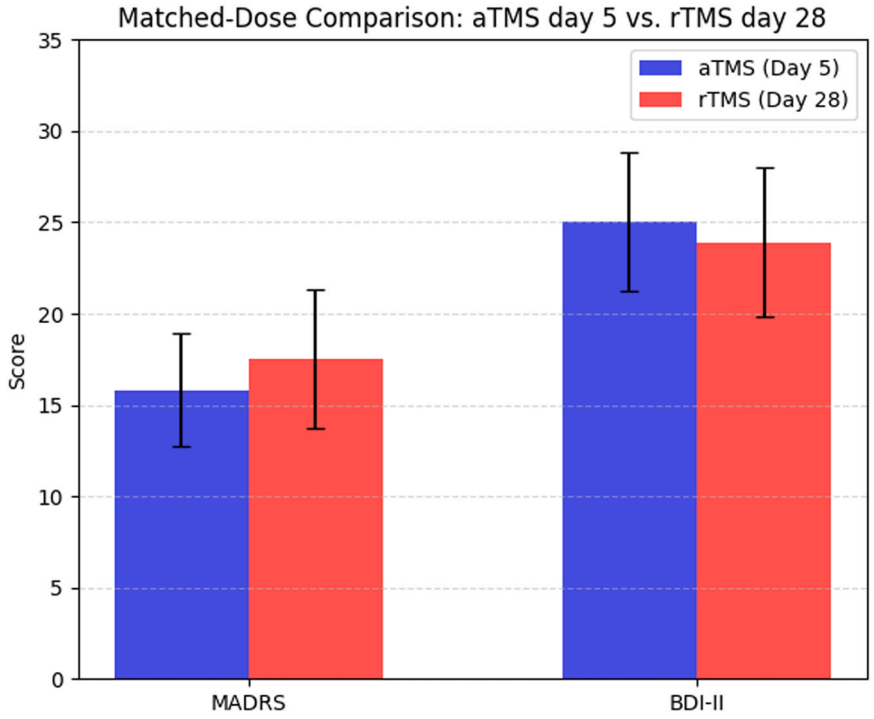


Fig. 4. Matched-Dose comparison of MADRS and BDI-II after 20 rTMS sessions (day 5 for aTMS vs. day 28 for rTMS).

George et al., who demonstrated that a high-dose accelerated approach could rapidly alleviate depressive symptoms, including in patients with acute suicidality (George et al., 2014). Moreover, the systematic review and meta-analysis by Sonmez et al. (2019) highlighted the consistent efficacy of aTMS, while also raising questions about the optimal protocol to maximize therapeutic response.

Unlike studies and reviews that primarily established the non-inferiority of aTMS vs. standard rTMS (Fitzgerald et al., 2018; van Rooij et al., 2024), our findings suggest that aTMS may offer a clinically meaningful advantage in faster symptom resolution. This is crucial, as one of the major challenges of antidepressant therapy is the latency of action, which can delay improvement for weeks. In severe cases of depression or suicidality, this delay can significantly impact outcomes, making the accelerated response observed with aTMS particularly valuable. Nevertheless, we also noted that by 28 days—when the standard group had completed 20 sessions—part of this gap narrowed, although aTMS still maintained a statistically significant lead on MADRS, suggesting both speed and overall efficacy benefits.

Interestingly, the same comparison (day 5 vs. day 28) for BDI-II did not reach statistical significance, indicating that self-reported symptoms converged more closely between the two arms by the 20th session. However, having comparable outcomes by day 5 vs. day 28 still highlights the advantage of achieving those results much earlier with an accelerated protocol.

Concerning its impact on suicidal symptoms, the accelerated protocol seems to represent a valuable alternative to the standard rTMS protocol, as it achieves comparable improvements in suicidal symptomatology within just 5 days of treatment compared to the 4 weeks required by the standard TMS protocol currently in use, without statistically significant differences observed between the two groups. This substantial reduction in treatment duration highlights the protocol's potential for addressing acute clinical needs while optimizing treatment efficiency and accessibility.

Notably, our subgroup analysis revealed no significant differences in the response trajectories of MDD vs. BD patients, suggesting that the observed TMS outcomes were not impacted by unipolar or bipolar diagnosis—though the small BD sample ($n = 9$) warrants caution in drawing definitive conclusions.

Regarding the limitations, this study was restricted by a total sample size of 33 patients, partly due to the unforeseen unavailability of the rTMS device, which was not predictable at the planning stage. Moreover, two early withdrawals in the standard rTMS group led to an analysis of 31 patients, resulting in uneven numbers (18 vs. 13). In addition, all patients were inpatients, which may limit the generalizability of findings to outpatient populations. Also, the BDI-II is a self-reported measure, and such subjective scales can introduce bias compared to clinician-rated instruments.

Secondly, the stimulation parameters and treatment course warrant further mention. The accelerated protocol was compared to a four-week course of standard rTMS, although some larger trials have employed six-week protocols (O'Reardon et al., 2007). Nonetheless, our choice of a four-week schedule is supported by numerous studies demonstrating its antidepressant efficacy and aligning with one of the FDA-cleared standards for rTMS. We specifically selected 4 weeks to match the total sessions (20) delivered in the aTMS arm, ensuring an equivalent number of pulses across groups. Notably, even under these conditions, aTMS outperformed standard rTMS in the early phase, underscoring its potential for rapid symptom alleviation. Additionally, the study was only single-blind. While raters assessing depression severity were blinded, patients were not, introducing possible bias despite efforts to minimize it by instructing them not to disclose treatment details.

In conclusion, if further investigations confirm these results, accelerated TMS (5 days vs. 4 weeks) could offer an effective alternative to conventional rTMS, providing faster response and remission. Our data show that aTMS had the most pronounced effects in the first 5 days - coinciding with its active phase - and that these clinical benefits extended to day 56, though the modest sample size and potential for delayed effects in standard rTMS must be considered. Achieving meaningful symptomatic relief more rapidly is especially relevant for patients who need urgent intervention, indicating that aTMS might address one of the major challenges in depression treatment: shortening the latency of therapeutic response, which remains a significant issue in pharmacological approaches.

The increased rapidity observed with aTMS also raises the possibility of exploring other shorter regimens. Such strategies might facilitate TMS treatments in a Day Hospital setting, optimizing health costs while maintaining efficacy. For instance, intermittent theta-burst stimulation (iTBS) offers shorter sessions (3 min vs. 19) (Berlim et al., 2017). A recent study (Dragon et al., 2025) explored accelerated iTBS (aiTBS) five times per day over five consecutive days vs. once per day for four weeks, with no significant differences in outcomes, suggesting comparable efficacy despite differing intensities.

However, larger multi-center, randomized, sham-controlled studies with greater statistical power are needed to confirm the short- and long-term safety and efficacy of accelerated TMS in both unipolar and bipolar Depressive Episodes, as well as to refine medication stability, blinding procedures, and stimulus parameters. In summary, our results indicate that rTMS can be effectively and safely administered with an accelerated intensive protocol, without increasing side effects or compromising tolerability.

CRediT authorship contribution statement

Cristina Colombo: Validation, Supervision. **Carolina Passani:** Methodology, Data curation. **Nicola Ragone:** Supervision, Investigation. **Barbara Barbini:** Project administration, Conceptualization. **Federico Seghi:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Michele Prato:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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