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No differences in treatment response between atypical depression and major depressive disorder after repetitive transcranial magnetic stimulation in a clinical sample

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ABSTRACT

Purpose: Repetitive transcranial magnetic stimulation (rTMS) is a treatment option for major depressive disorder (MDD). MDD is a heterogeneous condition with subtypes, including atypical depression (AD). The effectiveness of rTMS for AD remains unknown. In this study, we investigated the effects of rTMS in patients with AD compared to those with MDD in a clinical setting.

Materials and methods: A total of 103 patients with uni- or bipolar depressive episodes, treated with rTMS at the Uppsala Brain Stimulation Unit between April 2017 and October 2023, were included. Participants were categorized as AD (Quick Inventory of Depressive Symptomatology Self Report items 4, 7, and 9 ≥ 3) or MDD. The primary outcomes were response and remission rates based on the total score of Montgomery and Åsberg Depression Rating Scale self-report (MADRS-S). Response was defined as a 50% reduction of the total MADRS-S score and remission as MADRS-S < 10.

Results: Depressive symptoms significantly decreased after rTMS in the whole sample, with the mean MADRS-S score reduced from 34 to 25. The AD group had consistently lower scores on MADRS-S. No significant differences were observed in symptom reduction, response, or remission rates between AD and MDD groups. Response and remission rates were 12.6% and 2.9% for the whole sample, although reasons for treatment termination could not be assessed.

Conclusions: rTMS does not appear to yield specific benefits for AD. Observed response and remission rates were lower than previously reported, highlighting the need for more reports of the actual effectiveness of rTMS.

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Repetitive transcranial magnetic stimulation; major depressive disorder; atypical depression; response and remission

Introduction


Major depressive disorder (MDD) is a prevalent psychiatric condition characterized by substantial heterogeneity, with multiple subtypes classified based on clinical features, onset, and severity [1–4]. One such subtype is atypical depression (AD), first formally included as a diagnosis in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in 1994 [5]. Historically, AD was recognized as a depression subtype more responsive to monoamine oxidase inhibitors than tricyclic antidepressants [6,7]. In the fifth edition, AD is defined as a specifier for MDD, identified as “major depressive disorder with atypical features” [2].

AD is primarily characterized by mood reactivity (where mood brightens in response to positive events) and at least two of the following symptoms: significant weight gain or increased appetite, hypersomnia, leaden paralysis, and heightened interpersonal rejection sensitivity. These symptoms

must predominate during the most recent depressive episode or persistent depressive disorder, without overlapping with melancholic or catatonic depression features [2]. The prevalence of AD is estimated to 15–29% of MDD patients in epidemiological studies, while clinical reports suggest a prevalence of 18–36% [8], but the variation is high and dependent on various definitions [9]. The STAR*D trial, a large prospective study involving 4,041 patients with nonpsychotic depression, found hypersomnia, increased appetite, and weight gain to be twice as common in AD [10]. The same study also highlighted higher lifetime comorbidity rates of social phobia and panic disorder with agoraphobia in AD than in other depressive subgroups.

Depressive episodes are a dominant feature of bipolar disorder, contributing significantly to its overall burden [11]. An epidemiological study from 2012 suggested that features of atypical depression are more pronounced in bipolar depression compared to unipolar depression [12]. Furthermore, a 2015 study found all diagnostic symptoms of AD to be

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significantly more prevalent in bipolar depression than in unipolar depression or dysthymia [13].

Common depression rating scales, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) [14], tend not to assess atypical depressive symptoms. One way to address this limitation is by complementing the assessment with the 16-item Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16) [15], which aligns with DSM-IV criteria and includes atypical symptoms like hypersomnia, hyperphagia, and weight gain. To the best of our knowledge, there is no established scale for measuring atypical depression using DSM-5 criteria. The self-rated version MADRS-S [16] has been found comparable to MADRS [17]. Both the MADRS-S and QIDS-SR16 have demonstrated high internal consistency and validity in clinical settings [17,18]. Comparative studies between the QIDS-SR16 and MADRS have generally reported acceptable to high correlation coefficients and convergent validity, although most focus primarily on total scores [19–21]. More global and patient related measures are also a complement in treatment settings, and one such instrument is the EuroQol-Visual Analogue Scale (EQ-VAS) [22].

Despite the availability of various treatment options, a substantial proportion of MDD patients fail to respond adequately to treatment, with approximately one-third not achieving a response and two-thirds not achieving remission [23]. Efforts to improve outcomes through treatments tailored to MDD subtypes have yielded limited success [24,25]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment for depressive episodes that uses electromagnetic induction to modulate neuronal activity [26]. A copper coil placed on the scalp generates a magnetic field, inducing electrical currents in the brain. Treatment protocols vary by stimulation site, frequency, intensity, pulse number, and inter-pulse intervals. Standard protocols typically involve 20–30 sessions over four to six weeks [27]. Newer protocols, such as the intermittent theta-burst stimulation (iTBS), delivers bursts of 50Hz administered at 5Hz intervals, resulting in 600 pulses during 3–4min. Over the past two decades, rTMS has been validated as an effective and safe treatment, especially for treatment-resistant depression (TRD) – a condition defined by inadequate response to two antidepressant trials [28]. Most rTMS studies have focused on TRD populations, reporting response rates of 40–50% and remission rates of 25–30% in randomized controlled trials [29]. A large 2018 randomized clinical trial demonstrated that iTBS is non-inferior to high-frequency rTMS in effectiveness, safety, and tolerability [30]. A recent meta-analysis reinforced iTBS as a robust antidepressant intervention, particularly for its efficiency and therapeutic impact [31]. The Swedish National Board of Health and Welfare posits rTMS as a treatment that should be offered for moderate to severe MDD [32]. The most commonly used protocol in Sweden is iTBS [33].

A limited number of studies have investigated rTMS effects on atypical depressive symptoms such as hypersomnia, hyperphagia, and weight gain. A retrospective cohort study of 83 unipolar depression patients treated with high-frequency left-sided rTMS found significant reductions in these symptoms, although similar improvements were noted for insomnia and decreased appetite [34]. Another study of 17

adolescents with treatment-resistant depression showed a significant reduction in hypersomnia scores after 10 sessions and at six-month follow-up, with no observed effects on insomnia subscales [35].

It is thus unknown whether rTMS have certain beneficial effects in AD. This clinical cohort study sought to evaluate the effectiveness of rTMS in treating AD. Specifically, we aimed to compare response and remission rates between patients with AD and MDD treated with rTMS. We also aimed to determine whether atypical depressive symptoms were associated with treatment outcomes prior to initiating rTMS.

Material and methods

Participants

This naturalistic study was performed at Uppsala University Hospital, including a clinical sample of patients recruited between 19th of April 2017 and 17th of October 2023. During this period, all patients eligible for rTMS at the Brain Stimulation Unit at Uppsala University Hospital were approached regarding study participation. During the COVID-19 pandemic, Sweden did not apply strict lockdowns why the clinical patient flow during this time was not substantially affected. Eligibility for rTMS treatment at Uppsala Brain Stimulation Unit is limited to patients referred by open care psychiatry specialists. Inclusion criteria for the study were: age over 18 years, diagnosis of unipolar or bipolar depression, and written informed consent. Patients not eligible for rTMS treatment due to contraindications to the treatment, such as intracranial metal implants, other cranial implants, pacemaker or implanted cardiac defibrillator, vagus nerve stimulation, poorly controlled epilepsy, or ongoing substance use disorder, were excluded. The study received approval from the Research Ethical Review Board in Uppsala (registration number 2023-00332-01) and was conducted in accordance with the Declaration of Helsinki [36]. All participants gave informed consent to participate in the research.

Data collection and rTMS protocols

Data were extracted from each patient's medical record, including age at treatment initiation, sex, somatic and psychiatric diagnoses (ICD-10), history of suicide attempts, dates of rTMS treatments, number of treatments administered, and scores from psychiatric questionnaires. We were unable to collect information of which specific rTMS protocols that were used for each individual treatment. General information about the rTMS protocols used at the Uppsala Brain Stimulation Unit is provided below. The rTMS treatment was administered using either the MagPro R30 or MagPro X100 magnetic stimulators, equipped with the standard figure-of-eight coil Cool-B65 or the slightly angled B-70. Specific rTMS protocols differed between patients depending on diagnosis, comorbidity, side-effects, and practical circumstances. At the Uppsala Brain Stimulation Unit, patients diagnosed with unipolar depression receive at firsthand iTBS over the left dorso-lateral prefrontal cortex. Those diagnosed with bipolar depression, or those at increased risk of seizures or intolerant

to side-effects of left-sided iTBS, receive low frequency rTMS (1 Hz protocol) over the right dorsolateral prefrontal cortex. If no treatment response is observed after four weeks or severe side effects occur, the treatment protocol is terminated or changed. If changed, patients diagnosed with unipolar depression instead receive right-sided low frequency rTMS, and patients diagnosed with bipolar depression receives left-sided iTBS. Both treatment protocols require daily sessions on weekdays for four to six weeks, or until remission if weekly improvements are present. Treatment length varied, but all participants meeting the criteria of inclusion and exclusion were included in the descriptive statistics, regardless of the total length of their treatment period.

Rating scales

Per local clinical guidelines, all patients rated current depressive symptoms *via* questionnaires before initiation of rTMS, two weeks after initiation of rTMS, and furthermore weekly until end of treatment.

The MADRS-S contains the following items: mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism, and zest for life. Each item rates from 0 to 6, with 0 being interpreted as no current depressive symptoms and 6 as extreme symptoms of depression being present. The total score ranges from 0–54 [37].

The Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16) is a self-rating questionnaire of depressive symptoms during the past seven days. It consists of sixteen items rated from 0 to 3 on a Likert scale, where 0 is interpreted as not typical for depression and 3 supports depression. Total score ranges from 0 to 27 [15].

Lastly, patients were asked to answer the EQ-VAS, which is the patient's self-rated health rated from 0–100 on a visual analogue scale, where 0 represents the patient's worst imaginable health state and 100 the best imaginable state of health [38].

Operationalizing of atypical depression

To operationalize atypical depression the items of QIDS-SR16 that include atypical depression, i.e. hypersomnia {4}, hyperphagia {7}, and weight gain {9}, were used (QIDS-SR4,7,9). This specific clustering of atypical symptoms has been used in a previous study [34]. Participants were divided into subgroups based on their combined pre-treatment score of QIDS-SR4,7,9. Those with a combined score of QIDS-SR4,7,9 ≥ 3 at baseline were labeled as AD, whereas patients with a score ≤ 2 were labeled as MDD. The selection of QIDS-SR4,7,9 ≥ 3 as the study's cut off-value was chosen based on the scale's construct combined with the entire sample's median split of QIDS-SR4,7,9 equaling 2.

Statistical analyses

The primary outcomes were rates of response, defined as a 50% reduction of the total MADRS-S score, and remission, defined as MADRS-S < 10 at end of treatment [39]. Statistical

analyses were performed using R, version 4.5.1 [40]. Initially, all data were assessed for normal distribution. The data were then organized into tables containing frequencies, mean, standard deviation (SD) and percentages and reported according to STROBE guidelines [41]. Linear mixed-effects models were fitted using lme4 package [42] to examine the relationship between MADRS-S score and groups of AD and MDD. Fixed effects included diagnosis (AD or MDD), time point, and sex. Random effects included participant (subject) to account for repeated measures over time as well as random slopes for time point and diagnosis. Additionally, we tested a model with fixed-effects for comorbidity and medication. In order to assess dropout versus those that completed a linear mixed-effects model was fitted to examine the association between time point, status ("dropped" vs. completed rTMS), and their interaction on MADRS-S scores. Random intercepts were included for participants to account for repeated measurements. To further assess the association of type of diagnosis (AD or MDD) with treatment response we fitted a model with EQ-VAS as the dependent variable. We used the Akaike Information Criterion (AIC), the Schwarz Bayesian Criterion (BIC), Loglikelihood (LL) and Loglikelihood Ratio Test (LRT) to determine which model fit the data best. For the AIC, BIC and LL the model with the lowest value indicates the best fit while LRT was used to statistically compare nested models. The values of the indices are reported in [Supplementary table S2 and S4](#). We visually inspected the residual plots without obvious deviations from homoscedasticity or normality, therefore deeming the data appropriate to model with linear mixed-effects models for MADRS-S. The residual plots for EQ-VAS were found to be acceptable. Standardized parameters were obtained by fitting the model on a standardized version of the dataset. 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation.

Results

Demographic and clinical characteristics

A total of 162 patients fulfilled criteria of inclusion. Of these, 59 were excluded due to missing complete MADRS-S or/and QIDS-SR4,7,9 before the start of treatment. Consequently, 103 patients were ultimately included. Descriptive data are summarized in [Table 1](#). The age and gender distribution were similar across the two groups, with most participants being women. The mean age was 34.1 years for the AD group and 36.6 years for the MDD group. Most participants in both groups were diagnosed with unipolar depression. The AD group had twice as many patients diagnosed with bipolar depression compared to the MDD group. There were no substantial differences between concurrent medical treatments, apart from more mood stabilizers and lithium in the AD group. The AD group had lower scores on the MADRS-S at baseline (32.8 versus 35.1), but only marginal lower EQ-VAS (26.7 vs 28.2).

Treatment effect

The mean total number of treatments was 26 for the AD group and 27 for the MDD group. The median treatment

period was 38 days for the AD group and 44 days for the MDD group. There were no statistically significant differences in the distribution of these variables between the two

Table 1. Demographic and clinical baseline data of study participants.

	AD (n=51)	MDD (n=52)
Age, mean (SD)	34.1 (13.3)	36.6 (13.1)
Female, n (%)	31 (60.8)	32 (61.5)
MADRS-S total score, mean (SD)	32.8 (7.3)	35.1 (6.3)
QIDS-SR _{4,7,9} , mean (SD)	4.3 (1.5)	0.8 (0.9)
EQ-VAS, mean (SD)	26.7 (11.7) ^a	28.2 (15.1) ^a
Primary diagnosis n (%)		
Unipolar depression	41 (80.4)	47 (90.4)
Bipolar depression	10 (19.6)	5 (9.6)
Record of past suicide attempt, n (%)	13 (25.5) ^d	13 (25.0) ^d
Other concurrent diagnosis, n (%)		
Anxiety disorder ¹	14 (27.4)	13 (25.0)
Personality disorder ²	4 (7.8)	2 (3.8)
Neuropsychiatric disorders ³	5 (9.8)	4 (7.7)
Medication, n (%):		
Use of antidepressants ⁴	38 (74.5)	39 (75.0)
Use of antipsychotics ⁵	21 (41.2)	22 (42.3)
Use of mood stabilizers ⁶	9 (17.6)	6 (11.5)
Use of lithium	10 (19.6)	7 (13.5)
Use of benzodiazepines ⁷	13 (25.5)	13 (25.0)

Abbreviations: AD=Atypical depression, MDD=Major depressive disorder, IQR=Interquartile range, SD=Standard deviation, EQ-VAS=EuroQoL-Visual Analogue Scale, MADRS-S=Montgomery and Åsberg Depression Rating Scale Self-assessment, QIDS-SR_{4,7,9}=Quick Inventory of Depressive Symptomatology Self Report item 4, 7, and 9.

¹Anxiety disorders included diagnosed agoraphobia, social phobia, panic disorder, generalized anxiety disorder, mixed anxiety and depressive disorder, unspecified anxiety disorder, predominantly obsessional thoughts or ruminations, obsessive-compulsive disorder, acute stress reaction, post-traumatic stress disorder, body dysmorphic disorder.

²Personality disorders included emotionally unstable personality disorder, unspecified personality disorder.

³Neuropsychiatric disorders included childhood autism, atypical autism, overactive disorder associated with mental retardation and stereotyped movements, asperger syndrome, attention-deficit hyperactivity disorder, attention deficit disorder.

⁴Antidepressants included selective serotonin reuptake inhibitors (citalopram, escitalopram, sertraline, vortioxetine), serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), monoamine oxidase inhibitors (moclobemide, tranylcypromine), agomelatine, bupropion, clomipramine, and mirtazapine.

⁵Antipsychotics included aripiprazole, flupentixol, haloperidol, levomepromazine, lurasidone, olanzapine, quetiapine, and risperidone.

⁶Mood stabilizers included valproic acid and lamotrigine.

⁷Benzodiazepines included indefinite prescription of oxazepam or diazepam.

^aData was missing for 1 participant.

^bData was missing for 9 participants.

^cData was missing for 10 participants.

^dData was missing for 19 participants.

Table 2. Changes of MADRS-S and EQ-VAS scores during treatment, mean (SD).

	MADRS-S ₀	MADRS-S ₁	MADRS-S ₂	MADRS-S ₃	MADRS-S ₄	MADRS-S ₅
AD	32.8 (7.3) n=51	28.5 (8.0) n=42	26.2 (8.7) n=45	25.2 (8.3) n=42	25.4 (7.8) n=33	24.0 (8.8) n=23
MDD	35.1 (6.3) n=52	31.5 (7.1) n=43	30.9 (7.1) n=47	28.2 (7.8) n=45	27.7 (8.3) n=33	25.6 (9.3) n=26
	EQ-VAS-S ₀	EQ-VAS-S ₁	EQ-VAS-S ₂	EQ-VAS-S ₃	EQ-VAS-S ₄	EQ-VAS-S ₅
AD	26.7 (11.7) n=50	33.4 (14.0) n=42	35.7 (12.7) n=45	37.0 (11.7) n=42	40.3 (14.8) n=33	40.6 (15.2) n=21
MDD	28.2 (15.1) n=51	33.4 (16.8) n=42	34.1 (16.1) n=44	39.3 (17.4) n=43	37.9 (17.4) n=32	42.5 (17.7) n=25

Atypical depression (AD) defined as participants with QIDS-SR_{4,7,9} ≥ 3. MADRS-S₀ represents MADRS-S score at baseline, MADRS-S₁ two weeks after treatment initiation. Remaining MADRS-S₂₋₅ were collected weekly.

Atypical depression (AD) defined as participants with QIDS-SR_{4,7,9} ≥ 3. S0 represents measurement score at baseline, S1 two weeks after treatment initiation. Remaining measurements i.e. S2-5 were collected weekly. SD=Standard deviation, MADRS-S=Montgomery and Åsberg Depression Rating Scale Self-assessment, EQ-VAS=EuroQoL-Visual Analogue Scale, AD=Atypical depression, MDD=Major depressive disorder.

groups. The total number of treatments, total treatment period in days, and the median interval of evaluations for both the AD and MDD groups are detailed in [Supplementary table 1](#). As shown in [Table 2](#), the number of participants gradually decreased during the treatment course. The number of participants in the AD group decreased from 51 to 23 at the end of treatment, and in the MDD group from 52 to 26. We were unable to assess whether this was due to response, remission, side-effects, patient's choice or any other reason. Eleven patients had missing MADRS-S ratings post-treatment and were excluded for this reason. The mean MADRS-S score for the AD group decreased from 32.8 at the start of treatment to 24.0 at the end of treatment. For the MDD group, the mean MADRS-S score decreased from 35.1 to 25.6 over the same period. Five participants in the MDD group (9.6%) and eight in the AD group (15.7%) responded to the treatment. Three participants with AD (5.9%) reached remission while none in the MDD group did. No significant statistical differences were found between AD and MDD in terms of treatment response and remission rates. In the whole sample 12.6% responded to treatment, and 2.9% reached remission. Regarding EQ-VAS, participants in the AD group increased from 26.7 to 40.6, and in the MDD group from 28.2 to 42.5. No significant differences were observed between the groups.

Relationship between MADRS-S and EQ-VAS scores and group of AD and MDD

The likelihood ratio test indicated that the model with fixed effect for time point and diagnosis type with random effects for time point and participant had the best overall fit (see [supplementary table S2](#)). A model which included sex gave a slight improvement in fit however the change was small and non-significant. Sex was therefore not included in the final model. The models with fixed-effects for comorbidity and medication both had worse overall fit and were therefore not included in the final model (see [supplementary table S2](#)).

Findings from the linear mixed-effects model analysis are listed in [Table 3](#), showing an average reduction of MADRS-S total score of 1.8 between each time point. AD had a slightly lower estimated MADRS-S total score at baseline and subsequently across all time points. The model's total explanatory power was substantial (conditional R²=0.8) and the part related to the fixed effects alone (marginal R²) was of 0.2. The model's intercept, corresponding to baseline for MDD patients was at 34.6 (95% CI [32.7, 36.4], t(475) = 37.3, p < .001). The mixed-effects analysis provided no evidence that MADRS-S trajectories differed between participants who discontinued the study and those who completed it (see [Supplementary Table S4](#)).

We further fitted a linear mixed model to predict EQ-VAS with time point, see [Table 4](#). The model included time point as random effects. The effect of time point was statistically significant and positive (beta = 2.9, 95% CI [2.2, 3.7], t(464) = 7.7, p < .001; Std.beta = 0.31, 95% CI [0.2, 0.4]). The model's total explanatory power was substantial (conditional R²=0.8) and the part related to the fixed effects alone (marginal R²) was of 0.09.

Table 3. Linear mixed-effect model with MADRS-S as dependent variable with fixed effect diagnosis type (AD or MDD) and time point.

Fixed effects					
	<i>Estimate</i>	<i>SE</i>	<i>95% CI</i>	<i>t</i>	<i>p</i>
Intercept	34.6	0.9	32.7–36.4	37.3	<0.001
Time point	–1.8	0.2	–2.1 – –1.5	–11.0	<0.001
Diagnosis AD	–3.3	1.3	–5.8 – –0.8	–2.6	0.01
Random effects					
		<i>Variance</i>	<i>SD</i>	<i>Correlation</i>	
Participant (Intercept)		37.3	6.1		
Time point		1.3	1.1	0.03	
Residual		13.7	3.7		
Model fit					
<i>R</i> ²		<i>Marginal</i>	<i>Conditional</i>		
		0.2	0.8		

Random intercept for participant and random slope for time point. Abbreviations: MADRS-S=Montgomery and Åsberg Depression Rating Scale Self-assessment, SE=Standard error, CI=Confidence interval, AD=Atypical depression, SE=Standard Error, SD=Standard deviation.

Table 4. Linear mixed-effect model with EQ-VAS as dependent variable with time point as fixed effect. Random intercept for participant and random slope for time point.

Fixed effects					
	<i>Estimate</i>	<i>SE</i>	<i>95% CI</i>	<i>t</i>	<i>p</i>
Intercept	28.6	1.3	26.1–31.2	22.0	<0.001
Time point	2.9	0.4	2.2–3.7	7.7	<0.001
Random effects					
		<i>Variance</i>	<i>SD</i>	<i>Correlation</i>	
Participant (Intercept)		140.7	11.9		
Time point		8.9	3.0	–0.2	
Residual		50.9	7.1		
Model fit					
<i>R</i> ²		<i>Marginal</i>	<i>Conditional</i>		
		0.09	0.8		

Abbreviations: EQ-VAS=EuroQoL-Visual Analogue Scale, SE=Standard error, CI=Confidence interval, AD=Atypical depression, SE=Standard Error, SD=Standard deviation.

Discussion

In this clinical sample the AD group had significantly lower MADRS-S scores across all time points, with the same rate of decrease for both AD and MDD over time. Across the entire sample the mean MADRS-S score decreased by nine points after the treatment, but there were no differences between the groups. There were no differences between the groups in EQ-VAS scores before, during or after the treatment. This adds to the notion that the only observed difference between the groups were the expected lower MADRS-S scores in the AD group, which are likely due to that MADRS-S does not capture features of atypical depression, such as increased appetite and sleep.

Overall, 12.6% of the whole sample achieved treatment response, while only 2.9% reached remission. This is substantially lower than previous published response and remission rates. We were unable to assess the reasons why participants ended their treatment, and it might be that some achieved response and remission earlier and that our results are therefore artificially low. There is also a possibility however, that patients left the treatment course because they did not perceive an improvement.

A large naturalistic study of outpatients with MDD treated with rTMS reported a 56% response rate and 28% remission rate [43]. In another large sample from a rTMS registry, response rates were reported to be 58–83% and remission

rates 28–62% [44]. In a recent Swedish registry-based study, response and remission rates were 42% and 16% [39]. Another recently published review presented response and remission rates of 40–50% and 25–30% respectively [29], while similar response rates have been published regarding bipolar depression [45]. A randomized non-inferiority trial involving 414 patients compared the effectiveness of left-sided iTBS with standard left-sided 10Hz rTMS, reporting a response rate of 49% [30]. In contrast to our study, this study excluded many patients, e.g. those with bipolar disorder and other comorbid psychiatric conditions. Our cohort, drawn from a clinical sample, represents the population of patients treated with rTMS in Sweden. The presence of comorbidities and the severity of illness in our cohort may partially explain the lower response and remission rates observed. Additionally, the exclusion of 62 patients due to incomplete QIDS-SR16 and MADRS-S data before treatment initiation could have influenced our results.

Although our entire cohort showed a mean reduction in MADRS-S scores over time, the majority did not meet the defined criteria for treatment response. However, these patients still experienced symptom improvement during rTMS treatment, suggesting that even those classified as non-responders benefited from the intervention. It is also important to consider that response and remission as outcome measures do not account for patients whose condition worsens during treatment.

We have found no previously published study evaluating response and remission rates of patients diagnosed with AD treated with rTMS, making our results difficult to compare with other studies. While our results suggest a positive treatment response in the whole sample, it is important to note that the absence of a control group means we cannot disentangle the treatment effect from a placebo effect.

Although previous studies have indicated that left-sided high frequency rTMS could have an effect on symptoms of hypersomnia, hyperphagia and weight gain [46,47], these studies' cohorts have also shown similar effects on typical symptoms of depression (insomnia, hypophagia, and decreased weight). Our study only analyzed the total scores of MADRS-S, disregarding changes in QIDS-SR4,7,9, QIDS-SR16, and the trajectories of specific subscale items in both scales.

Limitations

The study sample was recruited from a clinical environment, which included a diverse group of patients with varied clinical characteristics and comorbidities. Also, confounders such as psychiatric comorbidities and concurrent medication have not been included in our analyses.

A major limitation of our study is the inability to retrieve information on the specific rTMS protocols used for individual patients. Although local guidelines specify which protocols are typically used for unipolar and bipolar depression, we cannot confirm the exact protocol applied to each patient, nor if alternative protocols were used. This lack of detailed protocol data limits our ability to precisely evaluate the treatment effects of specific protocols and compare

outcomes across different protocols and patient groups. In the light of this limitation, our results must be interpreted with caution.

The lack of reasons for drop-out or treatment termination is also a substantial limitation which needs to be considered when interpreting the results. We did not compute a last observation carried forward. This may have resulted in a larger confidence interval in our linear mixed model analysis. In general, the most common reason for clinical drop-outs in rTMS studies is side effects and physical discomfort, or insufficient symptom improvement. Overall, drop-out rates typically range from 7–12% in well-controlled trials, while real-world or naturalistic studies can report drop-out rates of up to 25–35% [48–50]. A recent Swedish register-based study reported a drop-out rate of 10.9% in clinical settings [39].

The use of non-validated rating scales, such as QIDS-SR4,7,9 limits the findings of this study. These scales, while derived from validated instruments, are not validated independently. However, the three items on excessive sleep (item 4), increased appetite (item 7), and weight gain (item 9) in the QIDS-SR16 are central to the concept of AD, and they are not captured by the MADRS-S (which only captures less sleep and appetite). Our study defined AD as QIDS-SR4,7,9 ≥ 3 , yielding a prevalence AD of 50%. Previous studies have estimated the prevalence of AD to 15–36% [8]. Thus, defining AD as QIDS-SR4,7,9 ≥ 3 may yield a too high prevalence. Notably, these items only captures three out of the six symptoms included in the DSM-5-TR criteria for AD [2]. Additionally, patient weight was not reported during treatment evaluation. Item nine of QIDS-SR16, which assesses increased weight, is subjective, and an objective weight measurement could have provided more reliable data.

Conclusion

In conclusion, our findings show no significant differences in rTMS treatment response and remission rates between patients with MDD and those labeled AD. Notably, the presence of atypical depressive symptoms were not associated with treatment outcome before initiation of rTMS. These results question the clinical utility of the AD concept in rTMS treatment settings. Lastly, the response and remission rates for the entire cohort were substantially lower than previously published studies, which potentially raises the question of the clinical effectiveness of rTMS. However, several factors may have influenced these results, including a small sample size, non-control of dropouts, variability in rTMS protocols, and the use of non-validated rating scales.

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Disclosure of interest

The authors report there are no competing interests to declare.

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