

Efficacy, Effectiveness, and Safety of Transcranial Magnetic Stimulation for Bipolar Depression: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) is cleared by the Food and Drug Administration for major depression, and recently received breakthrough status for bipolar depression (BDep). However, evidence on its efficacy and safety and optimal protocols for BDep remains limited. We conducted a systematic review to synthesize available data on rTMS for BDep.

METHODS: We systematically searched 4 literature databases for studies published between 1995 and 2025 treating participants with acute BDep (1097 articles). The primary outcome for the meta-analysis was change in mean depression severity scores from baseline. Determinants of treatment response were assessed using meta-regression and subgroup meta-analyses.

RESULTS: Fifty-six articles were included, representing a total of 1709 patients with BDep. Active TMS had superior antidepressant efficacy relative to sham in randomized controlled trials (RCTs) (Cohen's $d = 0.40$). Rates of treatment-emergent mania or hypomania were low and equivalent to those found for sham (odds ratio = 1.3; 95% CI, 0.7–2.4). A large effect size for antidepressant effectiveness was found when pooling active arms of RCTs with data from uncontrolled studies (Cohen's $d = 1.4$), with rates of response (46.81%) and remission (28.25%) similar to those described for MDD and preserved in subanalyses for high-frequency protocols, including intermittent theta burst stimulation (iTBS) delivered to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency protocols delivered to the right DLPFC. Higher baseline illness severity and more treatment sessions were predictors of greater antidepressant effect.

CONCLUSIONS: TMS is efficacious and safe in BDep, with response and remission rates on par with rates for unipolar depression. High- and low-frequency protocols on the left and right DLPFC, respectively, are robustly associated with positive outcomes, with left DLPFC iTBS showing noninferiority to more widely used high-frequency rTMS protocols.

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The global lifetime prevalence of bipolar disorder (BD) is estimated to be 2% (1–3), with depressive episodes representing 70% to 80% of symptomatic periods and contributing most strongly to disability (4,5). Unfortunately, there are few pharmacological treatments approved for bipolar depression (BDep) (6), with many patients failing to respond to available strategies and/or suffering from intolerable side effects, which further limits the available treatment options for this condition. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique cleared by the Food and Drug Administration (FDA) for episodes of major depression (7). The treatment works by modulating the activity of target brain regions using electromagnetic pulses, delivered by a coil placed over the patient's scalp (8). Different TMS protocols may facilitate or

inhibit neuronal activity in the targeted brain region. High-frequency (HF) protocols, such as >5-Hz standard rTMS or intermittent theta burst stimulation (iTBS) (3-pulse 50-Hz bursts, delivered at 5 Hz), are typically facilitatory, while low-frequency (LF) (1 Hz) standard rTMS and continuous TBS protocols are typically inhibitory (9).

Treatment with rTMS has been described as being better tolerated than other methods for treating major depression (10), because it is devoid of drug interactions and side effects commonly observed with pharmacological treatment strategies, such as antidepressants, mood stabilizers, and antipsychotics (11). Given this well-established safety and tolerability profile, as well as the lack of alternatives, rTMS has also been explored as a treatment option for BDep and was granted breakthrough status to treat BDep by the FDA (12).

However, there is controversy regarding the role of TMS in the management of BDep. Available sham-controlled trials testing the efficacy of TMS for BDep have had both positive (13,14) and negative (15) results.

Meta-analyses of the trials testing TMS for BDep support its superiority over sham (16,17). Real-world data are also indicative of effectiveness, with conflicting reports about whether effectiveness is superior (18) or inferior (19) to that observed in episodes of major depression. However, previous reviews and meta-analyses included a preponderance of studies with small or very small sample sizes and with substantial variability in the antidepressant effects of TMS across studies. Importantly, this has not allowed for analyses to inform on determinants of these effects, which could guide selection of the most appropriate treatment protocols or patients. Here, we conducted an updated systematic review to synthesize the evidence for TMS in BDep, using randomized controlled trials (RCTs) to assess efficacy and safety, and both controlled and uncontrolled trials for assessment of effectiveness. With the data for effectiveness, we further tested the TMS protocols and parameters, as well as patient characteristics, associated with greater response to treatment.

METHODS AND MATERIALS

See [Supplemental Methods](#) for details.

Protocol and Registration

The study was designed according to Cochrane recommendations (20) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (21), and published a priori in Prospero ([CRD42022330838](#)).

Information Sources and Search Strategy

The systematic literature review included randomized, sham-controlled trials, assessing the efficacy of TMS in patients with BDep, using depression severity rating scores and/or treatment response and/or remission rates, as defined by each study. For meta-regression analyses, only active arms of RCTs were considered, and open-label trials and retrospective studies were also included. Case reports, case series, and animal studies were excluded. Studies were identified through electronic searches in MEDLINE/PubMed, Web of Science, the Cochrane Library, and Embase databases. The search included publications from January 1, 1995, to May 2025. Filters were applied to restrict search results to adult human subjects ([Table S1](#)). Additionally, we searched reference lists of the initially selected studies, as well as of systematic reviews and meta-analyses, for additional eligible articles. Only articles in English, Spanish, French, Portuguese, or Mandarin were considered.

Study Selection and Eligibility Criteria

The studies identified in the literature search were independently selected by 2 researchers (FV and PF) in sequential phases of title, abstract, and full-text review, with consensus at the end of each step and disagreements resolved by a third researcher (GC). Only studies with participants age >18 years with BD and an ongoing episode of depression, as defined by the DSM (DSM-III or later edition) or its equivalent in the ICD

(ICD-9 or later editions), were included. Studies were excluded if they did not provide efficacy data regarding depression severity scores (mean and SD or SE) nor data regarding treatment response or remission rates, and such data were not provided upon request to the authors ([Table S2](#)). Studies reporting data from patients diagnosed with either BDep or unipolar depression were included only if BDep data could be isolated, either from the article or as provided after a request to the authors ([Table S2](#)).

Data Extraction, Data Items, and Risk of Bias

Data were independently extracted by 2 researchers (FV and PF), with disagreements resolved by a third researcher (GC). Details are provided in [Supplemental Methods](#). We contacted study authors to obtain or clarify missing information not reported in the published articles ([Table S2](#)), including clinical and/or demographic data ([Table S3](#)).

Study quality was defined by consensus between 2 researchers (FV and PF) according to the Cochrane RoB2 tool for randomized trials (22) and Newcastle-Ottawa Quality Assessment Scale for cohort studies (23). Each scale was divided into 3 levels (level 1 = high quality, level 2 = moderate quality, level 3 = low quality) to compute a single quality-related variable to test in meta-regression analyses.

Statistical Analysis

Analyses were conducted using Stata version 15 (StataCorp). We performed separate meta-analyses for treatment efficacy (from RCTs) and treatment effectiveness (from uncontrolled studies and active arms of controlled studies), excluding open-label RCT extensions to avoid bias from sequential TMS protocols. The primary efficacy outcome was the mean difference in depression severity between sham and active TMS; secondary outcomes included response and remission rates. Effectiveness analyses considered within-subject changes after active TMS. Standard deviations were imputed using validated formulas when not reported (20,24–26), and appropriate continuity corrections were applied for categorical outcomes (27). Effect sizes were reported using Cohen's *d* and odds ratios (ORs); number needed to treat (NNT) and number needed to harm (NNH) were calculated where relevant. Random-effects models were used (20,28). Publication bias was assessed via funnel plots and Egger's test and corrected using trim-and-fill methods. Subgroup meta-analyses and meta-regressions (only if ≥ 10 studies) were used to explore moderators of treatment effect (20).

RESULTS

Literature Review and Synthesis of Studies

The initial literature search yielded 1097 articles after removing duplicates. After title, abstract, and full-text review ([Figure 1](#)), 56 articles were eligible. Of these, 31 were RCTs (13–15,29–56), 17 were open-label clinical trials (57–73), and 8 were retrospective studies (18,19,74–79). A total of 1709 patients diagnosed with BDep were included in these studies, with several types of BD (351 with Bipolar I disorder, 418 with Bipolar II disorder, and 915 not classified/mixed). Of these, 1154 patients were treated with active TMS and 356 patients with sham TMS. In the active

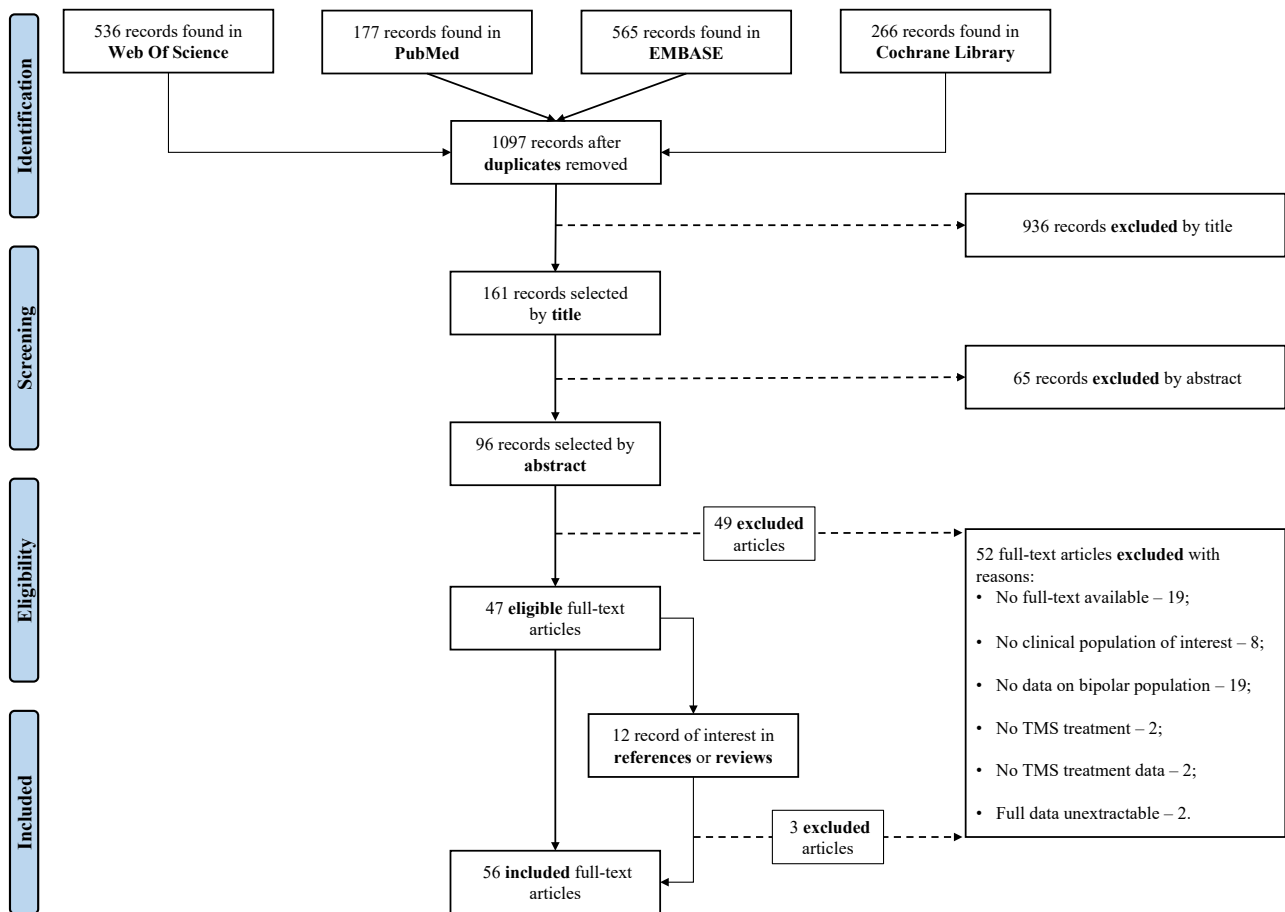


Figure 1. Article selection flowchart. A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21) and, from an initial pool of 1097 articles, after removing duplicates, 56 were included: 31 randomized controlled trials, 17 open-label clinical trials, and 8 retrospective studies. TMS, transcranial magnetic stimulation

group, the mean age at baseline was 44.7 ± 7.6 years, the mean duration of the current episode was 9.3 ± 6.18 months, the mean number of depressive episodes was 5.65 ± 3.49 , and the mean illness duration was 17.8 ± 5.9 years. In the sham group, the mean age at baseline was 42.1 ± 8.57 years, the mean length of the current episode was 8.7 ± 5.8 months, the mean number of depressive episodes was 6.1 ± 4.3 , and the mean duration of illness was 17.5 ± 3.8 years (Table 1). Among the 56 eligible studies, 28 also reported data from patients with unipolar depression (18,19,36–49,57–62,72,74–77,80). Twenty-eight studies included patients diagnosed with treatment-resistant BDp, and 51 studies reported concomitant medication, including mood stabilizers, reported in 45 articles (Table S4). Different TMS protocols were used across studies (Table S5). Risk of bias was moderate to low, and study quality was moderate to high (Tables S6 and S7).

Treatment Efficacy and Tolerability

When comparing sham to active TMS, we found a significant effect favoring active TMS (Cohen's $d = 0.40$; 95% CI, 0.16–0.63; $p = .001$; $n = 20$) (Figure 2A). The overall OR for

response was 2.10 (95% CI, 1.43–3.09; $p < .001$; $n = 30$; NNT = 8) (Figure 2B) and for remission was 2.26 (95% CI, 1.39–3.68; $p = .001$; $n = 17$; NNT = 9) (Figure 2C). Findings were consistent in the sensitivity analyses excluding studies where we used the strategies described in Methods and Materials to account for potential mathematical constraints (data not shown). Dropout rates were similar in the active and sham interventions (OR = 0.93; 95% CI, 0.54–1.58; $p = .8$; $n = 17$) (Figure 2D).

The number of available studies allowing for assessment of publication bias was 56 (81), and visual inspection of funnel plots suggested potential publication bias (Figure S1). Egger's tests supported the presence of publication bias only for the response rate meta-analysis ($p = .02$) but not the meta-analyses for depression score improvement ($p = .5$), remission rate ($p = .3$), and dropout rate ($p = .6$). Importantly, the Trim-Fill Duval-Tweedie test yielded unchanged effect sizes for the depression improvement score (Cohen's $d = 0.40$; 95% CI, 0.16–0.63) and dropout rate meta-analyses (OR = 1.13; 95% CI, 0.60–1.66) and increased ORs for response rate (3.58; 95% CI, 2.51–4.64) and remission rate (3.98; 95% CI, 1.98–5.98), supporting that the results are robust to

Table 1. Summary Table for the Eligible Studies

Study	Sham-Control Study	Total Sample Active Sham	TRD Criteria	Scale ^a	Baseline Depression Severity, Mean (SD)	Final Depression Severity, Mean (SD)	Response, % Patients	Remission, % Patients	Dropouts, <i>n</i>	Weeks of Response
					Active Sham	Active Sham	Active Sham	Active Sham	Active Sham	
Kimbrell <i>et al.</i> , 1999 (39), 20 Hz	Yes	3 1	No	HDRS-17	30 (0.1) 22 (0.1)	34.5 (0.1) 24 (0.1)	0.00% 0.00%	–	–	2
Klein <i>et al.</i> , 1999 (40)	Yes	7 6	No	HDRS-17	–	–	71.43% 16.67%	–	–	2
	–	–	–	MADRS	–	–	–	–	–	–
George <i>et al.</i> , 2000 (41)	Yes	7 2	No	HDRS-21	–	–	71.43% 0.00%	–	–	2
Dolberg <i>et al.</i> , 2002 (29)	Yes	10 10	No	HDRS	22.00 (4.80) 25.50 (7.50)	15.70 (4.80) 21.30 (5.30)	–	–	–	2
Loo <i>et al.</i> , 2003 (42)	Yes	2 1	Yes	MADRS	–	–	0.00% 0.00%	–	–	3
Nahas <i>et al.</i> , 2003 (30)	Yes	11 12	No	HDRS-28	32.50 (4.30) 32.80 (7.60)	24.40 (10.40) 24.60 (10.70)	36.00% 33.00%	9.00% 8.30%	0 0	2
Rossini <i>et al.</i> , 2005 (43)	Yes	12 5	Yes	HDRS-21	–	–	50.00% 20.00%	–	–	2
Su <i>et al.</i> , 2005 (44)	Yes	3 2	Yes	HDRS-21	–	–	66.60% 50.00%	–	–	2
Fitzgerald <i>et al.</i> , 2006 (36)	Yes	4 4	Yes	MADRS	–	–	50.00% 25.00%	–	–	4
Fitzgerald <i>et al.</i> , 2006 (58), 1 Hz	No	12	Yes	HDRS-17	–	–	41.60%	–	–	4
Fitzgerald <i>et al.</i> , 2006 (58), 2 Hz	No	13	Yes	HDRS-17	–	–	92.00%	–	–	4
McDonald <i>et al.</i> , 2006 (45)	Yes	5 3	Yes	HDRS-21	–	–	20.00% 0.00%	–	–	2
Herwig <i>et al.</i> , 2007 (37)	Yes	7 4	Yes	MADRS	27.70 (4.86) 27.50 (9.86)	15.20 (11.95) 22.60 (5.130)	60.00% 30.00%	60.00% 0.00%	2 1	3
	–	–	–	HDRS	22.85 (3.48) 24.75 (8.49)	16.20 (17.60) 17.60 (5.510)	–	–	–	3
	–	–	–	BDI	25.14 (6.50) 23.25 (12.40)	17.80 (16.02) 22.33 (8.50)	–	–	–	3
Dell'Osso <i>et al.</i> , 2009 (64)	No	11	No	HDRS-21	–	–	54.50%	36.36%	0	3
Paillière Martinot <i>et al.</i> , 2010 (46)	Yes	11 5	Yes	MADRS	–	–	54.55% 20.00%	–	–	2
Harel <i>et al.</i> , 2011 (63)	No	19	No	HDRS-24	31.00 (12.00)	15.80 (2.91)	63.20%	52.60%	2	5
Hernández-Ribas <i>et al.</i> , 2013 (47)	Yes	5 1	Yes	HDRS-21	–	–	100.00% 100.00%	–	–	3
Ning <i>et al.</i> , 2013 (54)	Yes	30 29	No	HDRS-24	46.10 (7.60) 46.40 (7.50)	10.30 (3.00) 12.60 (5.30)	96.70% 93.10%	73.30% 44.80%	3 5	4
Beynel <i>et al.</i> , 2014 (31)	Yes	5 7	Yes	MADRS	32.00 (5.00) 30.00 (6.00)	13.00 (6.00) 14.00 (11.00)	80.00% 57.00%	0.00% 28.57%	–	1–3

Table 1. Continued

Study	Sham-Control Study	Total Sample	TRD Criteria	Scale ^a	Baseline Depression Severity, Mean (SD)	Final Depression Severity, Mean (SD)	Response, % Patients	Remission, % Patients	Dropouts, <i>n</i>	Weeks of Response
		Active Sham			Active Sham	Active Sham	Active Sham	Active Sham	Active Sham	
Speer <i>et al.</i> , 2014 (38), L-HF	Yes	6 2	Yes	HDRS-28	35.60 (13.10) 27.50 (7.70)	27.50 (9.10) 28.00 (0.00)	0.00% 0.00%	0.00% 0.00%	0 1	3
Chistyakov <i>et al.</i> , 2015 (48)	Yes	6 4	–	HDRS-21	–	–	50.00% 0.00%	–	–	2
Prasser <i>et al.</i> , 2015 (49), LF/HF	Yes	4 6	–	HDRS-21	–	–	25.00% 33.33%	–	–	3
Prasser <i>et al.</i> , 2015 (49), cTBS/iTBS	Yes	8 6	–	HDRS-21	–	–	12.50% 33.33%	–	–	3
Carnell <i>et al.</i> , 2016 (57)	No	50	No	HDRS-17	20.26 (5.97)	12.38 (7.21)	34.00%	26.00%	0	–
Fitzgerald <i>et al.</i> , 2016 (32)	Yes	22 23	Yes	HDRS-17	23.20 (4.0) 23.00 (5.10)	19.80 (5.70) 20.00 (4.80)	13.64% 4.350%	9.09% 0.00%	4 2	4
Hu <i>et al.</i> , 2016 (33), L-HF	Yes	11 12	No	MADRS	36.50 36.00	15.50 17.50	72.00% 66.60%	27.30% 16.60%	1 1	4
	–	–	–	HDRS-17	29.00 29.00	10.50 12.50	–	–	–	–
Hu <i>et al.</i> , 2016 (33), R-LF	Yes	12 12	No	MADRS	39.50 36.00	14.50 17.50	75.00% 66.60%	16.60% 16.60%	1 1	4
	–	–	–	HDRS-17	31.00 29.00	11.00 12.50	–	–	–	–
Kazemi <i>et al.</i> , 2016 (67), R-LF and L-HF	No	15	No	BDI-II	31.60 (7.70)	12.73 (11.22)	80.00%	40.00%	0	3
Kazemi <i>et al.</i> , 2016 (67), R-LF	No	15	No	BDI-II	30.20 (9.30)	18.13 (14.57)	47.00%	40.00%	0	3
Rostami <i>et al.</i> , 2017 (62)	No	146	No	BDI-II	32.61 (9.59)	16.09 (11.14)	41.00%	–	0	–
Tavares <i>et al.</i> , 2017 (13)	Yes	25 25	Yes	HDRS-17	25.80 (5.25) 25.32 (3.76)	13.50 (9.41) 18.26 (9.88)	54.55% 26.00%	31.82% 17.40%	5 2	4
Desbeaumes Jodoin <i>et al.</i> , 2018 (75)	No	16	Yes	MADRS	21.13 (8.50)	14.38	37.50%	37.50%	–	4
Kazemi <i>et al.</i> , 2018 (66)	No	20	No	BDI-II	30.15 (10.05)	–	55.00%	15.00%	0	2
Rapinesi <i>et al.</i> , 2018 (61)	No	20	Yes	HDRS-17	22.90 (3.37)	10.85 (3.60)	80.00%	10.00%	0	4
Bulteau <i>et al.</i> , 2019 (34)	Yes	12 14	Yes	MADRS	30.00 (5.69) 28.21 (5.35)	14.92 (11.63) 15.29 (10.14)	66.67% 50.00%	41.67% 28.57%	0 1	3
	–	–	–	BDI-13	20.50 (6.05) 19.60 (4.35)	12.33 (9.55) 10.23 (7.05)	–	–	–	–
Kito <i>et al.</i> , 2019 (59), ITI = 11 s	No	6	–	QIDS-16	–	–	50.00%	50.00%	0	4–6
Kito <i>et al.</i> , 2019 (59), ITI = 26 s	No	5	–	QIDS-16	–	–	80.00%	80.00%	0	4–6

Table 1. Continued

Study	Sham-Control Study	Total Sample Active Sham	TRD Criteria	Scale ^a	Baseline Depression Severity, Mean (SD)	Final Depression Severity, Mean (SD)	Response, % Patients	Remission, % Patients	Dropouts, <i>n</i>	Weeks of Response
					Active Sham	Active Sham	Active Sham	Active Sham	Active Sham	
Goldwaser <i>et al.</i> , 2020 (78)	No	39	No	MADRS	–	–	69.00%	36.00%	5	6
Olejarczyk <i>et al.</i> , 2020 (60)	No	10	Yes	MADRS	23.28 (2.50)	11.70 (5.40)	60.00%	–	–	4
Phillips <i>et al.</i> , 2020 (79)	No	17	Yes	QIDS-16	18.59 (5.06)	10.70	65.00%	35.00%	0	6
Mak <i>et al.</i> , 2021 (59)	Yes	23 25	Yes	MADRS	26.80 (4.90) 26.20 (3.80)	17.15 (5.45) 17.95 (5.48)	13.00% 12.00%	4.35% 4.00%	3 3	3
McGirr <i>et al.</i> , 2021 (15)	Yes	18 19	Yes	MADRS	32.27 (4.04) 31.52 (5.22)	24.46 (10.58) 23.06 (10.82)	20.00% 18.75%	20.00% 18.75%	2 4	4
Yang <i>et al.</i> , 2021 (19)	No	13	No	HDRS-21	18.20 (1.39)	13.56	7.70%	–	0	2–6
Alhelali <i>et al.</i> , 2022 (74)	No	46	No	HDRS-21	22.00 (8.00)	15.00	33.00%	30.00%	0	4
Gama-Chonlon <i>et al.</i> , 2022 (18), 10 Hz	No	20	–	PHQ-9	–	–	16.00%	9.00%	–	–
Gama-Chonlon <i>et al.</i> , 2022 (18), R-LF and L-HF	No	7	–	PHQ-9	–	–	2.00%	0.00%	–	–
Gama-Chonlon <i>et al.</i> , 2022 (18), Mixed	No	7	–	PHQ-9	–	–	0.00%	0.00%	–	–
Koutsomitros <i>et al.</i> , 2022 (68)	No	23	–	BDI	26.26	14.83	–	61.00%	4	4
Zengin <i>et al.</i> , 2022 (35)	Yes	14 15	Yes	HDRS-21	20.40 (2.80) 20.10 (2.60)	14.20 (5.70) 16.80 (2.80)	28.60% 6.70%	–	0 0	2
	–	–	–	BDI	34.00 (12.20) 29.50 (7.20)	24.60 (16.80) 26.20 (7.60)	–	–	–	–
Bouaziz <i>et al.</i> , 2023 (77), 1 Hz	No	3	Yes	MADRS	23.33 (4.04)	13.33 (11.93)	1.00%	1.00%	–	2–6
Bouaziz <i>et al.</i> , 2023 (77), 10 Hz	No	38	Yes	MADRS	25.47 (6.80)	15.63 (10.40)	17.00%	11.00%	–	4–6
Bouaziz <i>et al.</i> , 2023 (77), 20 Hz	No	20	Yes	MADRS	29.20 (6.38)	23.30 (8.88)	1.00%	2.00%	–	2–3
Bouaziz <i>et al.</i> , 2023 (77), iTBS	No	52	Yes	MADRS	25.92 (5.96)	19.15 (9.03)	13.00%	11.00%	–	2–4
Mallik <i>et al.</i> , 2023 (52)	Yes	11 8	–	HDRS-21	27.64 (9.05) 26.25 (9.16)	20.55 (7.34) 19.88 (9.66)	54.50% 50.00%	–	1 1	2
	–	–	–	BDI	35.73 (9.54) 36.75 (8.03)	28.27 (9.23) 28.75 (12.23)	–	–	–	–

Table 1. Continued

Study	Sham-Control Study	Total Sample Active Sham	TRD Criteria	Scale ^a	Baseline Depression Severity, Mean (SD)	Final Depression Severity, Mean (SD)	Response, % Patients	Remission, % Patients	Dropouts, <i>n</i>	Weeks of Response
					Active Sham	Active Sham	Active Sham	Active Sham	Active Sham	
Aaronson <i>et al.</i> , 2024 (65)	No	31	–	MADRS	33.7 (5.4)		27.00%	23.00%	1	5
Ikawa <i>et al.</i> , 2024 (74)	No	20	Yes	HDRS-21	21.40 (3.5)	8.20	75.00%	70.00%	0 0	6
	–	–	–	MADRS	31.40 (6.4)	10.5	–	–	–	–
Dellink <i>et al.</i> , 2024 (53)	Yes	18 19		HDRS-17	21.9 (3.9) 22 (3.0)	17.75 (5.25) 18.75 (3.75)	11.10% 5.30%	–	2 0	1
Li <i>et al.</i> , 2024 (69)	No	10	Yes	MADRS	–	–	–	–	0	1
Novák <i>et al.</i> , 2024 (51), RVL	Yes	20 20	Yes	MADRS	27.6 (5.5) 26.9 (4.3)	15.9 (4.24) 19.7 (4.18)	25.00% 15.00%	15.00% 10.00%	4 5	4
Novák <i>et al.</i> , 2024 (51), LDL	Yes	20 20	Yes	MADRS	26.2 (4.2) 26.9 (4.3)	14.8 (4.31) 19.7 (4.18)	40.00% 15.00%	35.00% 10.00%	5 5	4
Raj <i>et al.</i> , 2024 (70)	No	7	Yes	MADRS	40.0 (9.8)	5.70 (10.7)	5.00%	5.00%	0	1
Sheline <i>et al.</i> , 2024 (14)	Yes	12 12	Yes	MADRS	30.4 (4.80) 28.0 (5.40)	10.5 (6.70) 25.3 (6.7)	67.00% 33.00%	50.00% 0.00%	0 0	0.7
Appelbaum <i>et al.</i> , 2025 (56)	Yes	5 8	Yes	MADRS	30.2 (9.5) 29.0 (4.8)	14.0 (11.4) 24.6 (9.9)	40.00% 12.50%	–	0 0	1
d'Andrea <i>et al.</i> , 2025 (71)	No	10	–	MADRS	33.25 (7.94)	23.45 (8.86)	15.00%	5.00%	0	1
Trapp <i>et al.</i> , 2025 (55)	Yes	7 14	No	MADRS	15.9 (4.5) 21.8 (6.9)	10 (6.2) 9.5 (6.3)	42.86% 64.29%	71.43% 64.29%	–	1
Wu <i>et al.</i> , 2025 (72)	No	15	–	HDRS-24	25.13	11.73	60.00%	33.33%	0	4
Yu <i>et al.</i> , 2025 (73)	No	30	–	HDRS-17	19 (12.13)	12 (7.25)	30.00%	40.00%	0	2

BDI, Beck Depression Inventory; cTBS, continuous theta burst stimulation; HDRS, Hamilton Depression Rating Scale; HF, high-frequency; iTBS, intermittent theta burst stimulation; ITI, intertrial interval; L, left; LDL, left dorsolateral; LF, low-frequency; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ, Patient Health Questionnaire; QIDS, Quick Inventory of Depressive Symptomatology; R, right; RVL, right ventrolateral; TRD, treatment-resistant depression.

^aFor studies using more than 1 rating scale to assess depression severity, the following priority was considered whenever possible: HDRS > MADRS > BDI > QIDS.

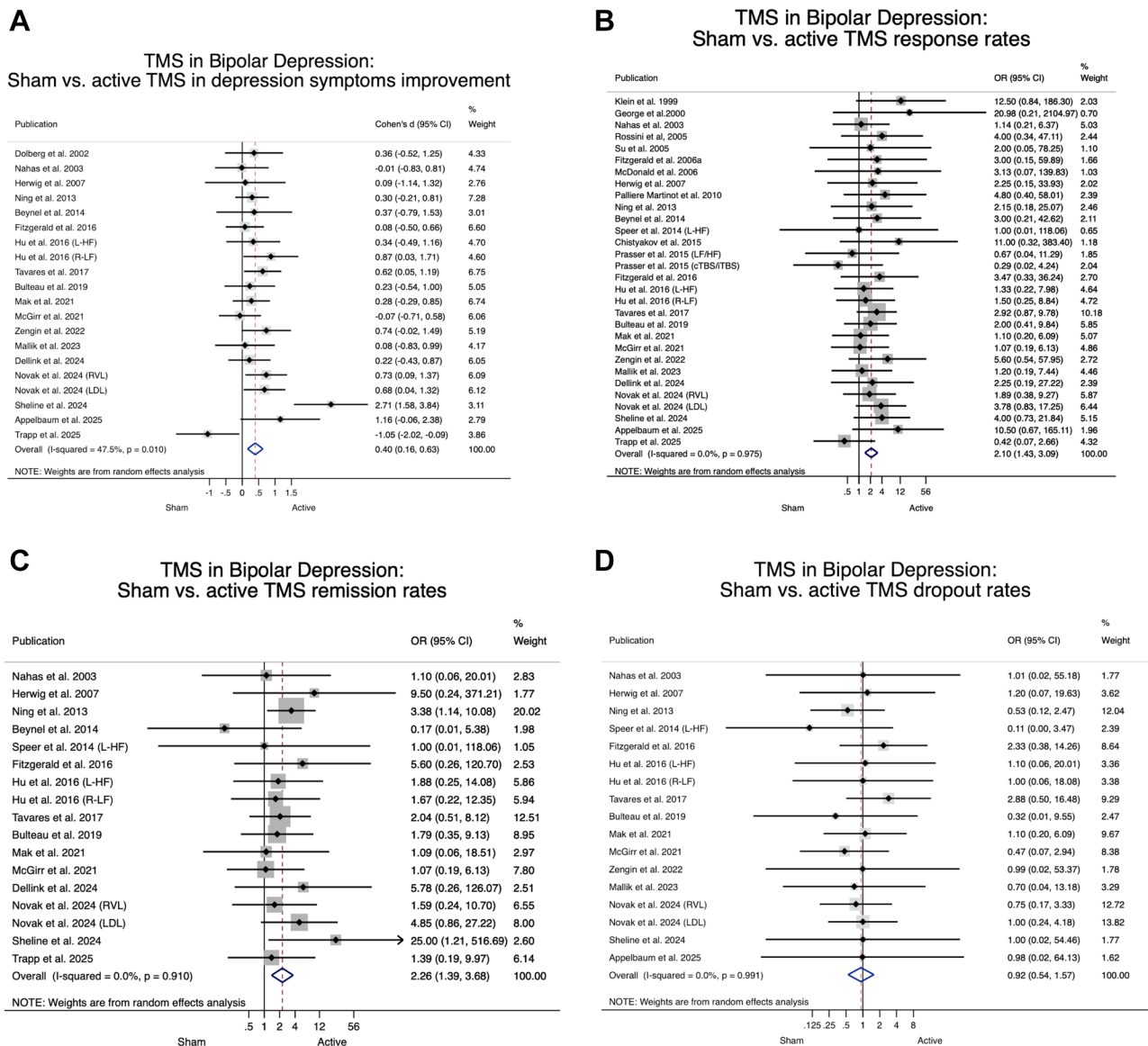


Figure 2. Forest plots of random-effects meta-analyses. There is a significant effect of transcranial magnetic stimulation (TMS) on depressive symptom severity when compared with sham (**A**). Response and remission rates favor active treatment over sham (**B, C**). Dropout rates were similar between active and sham (**D**).

publication bias. Finally, we confirmed that no specific study drove the results by performing leave-one-out meta-analyses.

Treatment-emergent hypomania/mania was reported in 16 patients, 9 in the active group (15,50,51) and 4 in the sham group (50,51). In such cases, patient characteristics, such as bipolar subtype, were not specified. All affected patients were receiving either mood stabilizers (15,50) or second-generation antipsychotics (51). A single case of TMS-induced generalized seizure was reported among the included studies (63). The event occurred on the 12th day of treatment in a patient treated with an H1-coil at 120% of resting motor threshold. The seizure lasted <10 seconds and was followed by approximately 30 seconds of postictal confusion and

amnesia, which resolved spontaneously. At the time of study entry, the patient was taking lithium, with a plasma concentration of 0.79 mmol/L (63). Other side effects, such as mild headaches, local sensitivity, fatigue, sleepiness, and insomnia, were mild and were reported more frequently (13,33,35–37,41–43,49,52,55,56,62,64,69–73,75,76,80,82).

Treatment Effectiveness

Given the evidence to support efficacy and tolerability of rTMS for BDep, we also aimed to summarize available data to inform real-world use of TMS in BDep. Therefore, we performed meta-analyses pooling data from active arms of sham-controlled trials with data from uncontrolled studies. For

analysis purposes, studies were divided into more than 1 active arm in articles comparing effects of distinct rTMS protocols, namely Fitzgerald *et al.* (36), assessing 1- and 2-Hz rTMS protocols over the left DLPFC; Speer *et al.* (38), evaluating 20- or 1-Hz protocols over the left DLPFC; Hu *et al.* (33) testing 10-Hz rTMS to the left DLPFC or 1-Hz rTMS to the right DLPFC; Kazemi *et al.* (67), comparing bilateral with 1-Hz rTMS over the right DLPFC; Kito *et al.* (59) comparing 2 left DLPFC protocols with different intertrain intervals (26 s vs. 11 s); Gama-Chonlon *et al.* (18) testing HF left-side stimulation, bilateral stimulation, and a mixed protocol; Bouaziz *et al.* (77) comparing 1-Hz stimulation of the right DLPFC and 10-, 20-, or 50-Hz stimulation of the left DLPFC; and Novak *et al.* (51), testing 10-Hz rTMS applied to the right ventrolateral PFC or left DLPFC.

Across studies and study arms, TMS had an overall significant effect on reduction of depression symptom severity (Cohen's $d = 1.40$, 95% CI, 1.21–1.59; $p < .001$; $n = 46$) (Figure 3A). The mean rate of treatment response was 46.81% (95% CI, 35.64–57.98; $p < .001$; $n = 65$), and the mean rate of remission was 28.25% (95% CI, 23.34–33.16; $p < .001$; $n = 46$) (Figure 3B, C). Additional analyses were performed to explore the impact of specific TMS protocol types on each of these three treatment outcomes. Left-sided HF-rTMS and right-sided LF-rTMS, both with 10 or more studies, were significantly associated with antidepressant effects across outcomes.

Left-sided iTBS, as well as right-sided LF-rTMS followed by left-sided HF-rTMS, despite fewer studies being available, also showed a significant treatment effects across outcomes. The remaining protocols did not provide sufficient evidence and/or consistent results across outcomes (Table 2).

Determinants of Antidepressant Effect

When we considered continuous sociodemographic and clinical variables from the pooled RCT and uncontrolled data (Table S3), meta-regressions revealed that baseline depression severity was significantly associated with greater antidepressant effect ($\beta = 0.23 \pm 0.07$, $p < .005$, $n = 46$). On the other hand, longer illness duration was associated with worse remission rates ($\beta = -1.99 \pm 0.96$, $p = .05$, $n = 18$), but with borderline statistical significance (Table 3). We did not find significant associations between antidepressant effect and bipolar disease type, mean age, or female sex (Table 3). Meta-regression analysis also revealed that TMS was effective irrespective of inclusion of patients with treatment-resistant depression (TRD) in the studies (Table 4). To assess the potential impact of mood stabilizers on TMS effectiveness, we conducted a meta-regression comparing studies that reported the use of these medications with those that did not use them or did not report their use (see Table S4). There were no differences in overall depression improvement ($\beta = -0.16 \pm 0.35$, $p = .65$, $n = 46$), response ($\beta = 6.68 \pm 9.21$, $p = .471$, $n = 65$), or remission rates ($\beta = -3.03 \pm 8.86$, $p = .734$, $n = 46$) among studies reporting the use of mood stabilizers (Table 4). Study quality was negatively associated only with remission rate ($\beta = -16.08 \pm 7.11$, $p < .05$, $n = 46$) (Table 3). Study design was not a significant predictor of antidepressant effect (Table 4).

While higher number of sessions was associated with improvement of depression severity ($\beta = -0.04 \pm 0.02$, $p = .02$,

$n = 40$), we did not find significant associations between antidepressant effect and number of pulses or trains per session, intertrain interval, or stimulation intensity (Table 3). Meta-regression analyses for binary TMS parameters showed that this is an effective antidepressant treatment irrespective of the method to determine motor threshold, targeting method, use of accelerated protocols, frequency, laterality, and side of stimulation (Table 4). Furthermore, a meta-regression comparing left DLPFC standard HF-rTMS (reference) to left DLPFC iTBS did not reveal significant differences, indicating that both protocols were equally effective (Table 4).

DISCUSSION

TMS is a well-established treatment for several psychiatric disorders, based on consolidated regulatory approvals and evidenced-based guidelines (7). Nonetheless, and despite meta-analyses indicating that it is efficacious and safe, the use of TMS in BDep is still questioned (16,17), largely because of conflicting results regarding its efficacy in sham-controlled trials (13,15). Despite originating largely from small samples, this balance has fueled the debate regarding the place of rTMS in the management of BDep, regardless of real-world data attesting its safety and efficacy (18,65).

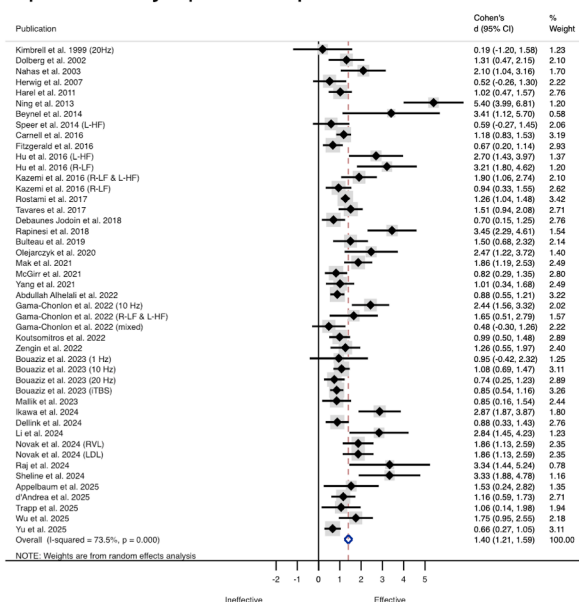
Contributing toward the determination of the role of TMS for treatment of BDep, our data provide definitive evidence of a statistically significant effect over sham, supporting efficacy, and with a large effect size (>0.8) supporting therapeutic effectiveness (83). To our knowledge, this is the largest dataset to date to yield response and remission rates (47% and 28%, respectively) that are similar to those reported for major depressive disorder (MDD) (84,85). Importantly, for the first time, we have also identified clear stimulation parameters and clinical characteristics associated with enhanced antidepressant effects in this population. Nevertheless, it is important to highlight that effectiveness estimates derived from non-randomized or real-world research, are more prone to reflecting nonspecific effects such as placebo response or regression to the mean, and should be interpreted with caution.

Our results confirm a clear and significant effect of TMS on depressive symptom severity in patients with BDep, similar to what has been found in unipolar depression (84). However, contrary to existing data establishing the durability of treatment effects in MDD (86), we found insufficient data to appropriately determine how long after TMS antidepressant effects last in BDep. This is particularly important given reports of transient effects in a large RCT, showing that active TMS was superior to sham at the end point (4 weeks) but not at follow-up (8 weeks) (13). In contrast, Rapinesi *et al.* (61) provided 6-month follow-up data to support sustained antidepressant effects of rTMS in BDep, while Koutsumitros *et al.* (68) showed rates of 78% symptom remission at 1-month follow-up. Regarding accelerated TMS protocols, accelerated iTBS and accelerated rTMS (arTMS) showed a sustained reduction in depression severity at 1 (56,69,70) and 3 (71,72) months of follow-up, respectively. In the future, studies evaluating the durability of the antidepressant effect in BDep should be conducted to complement existing knowledge.

We also extracted data concerning tolerability and safety. As in unipolar depression (87), the data collected here support

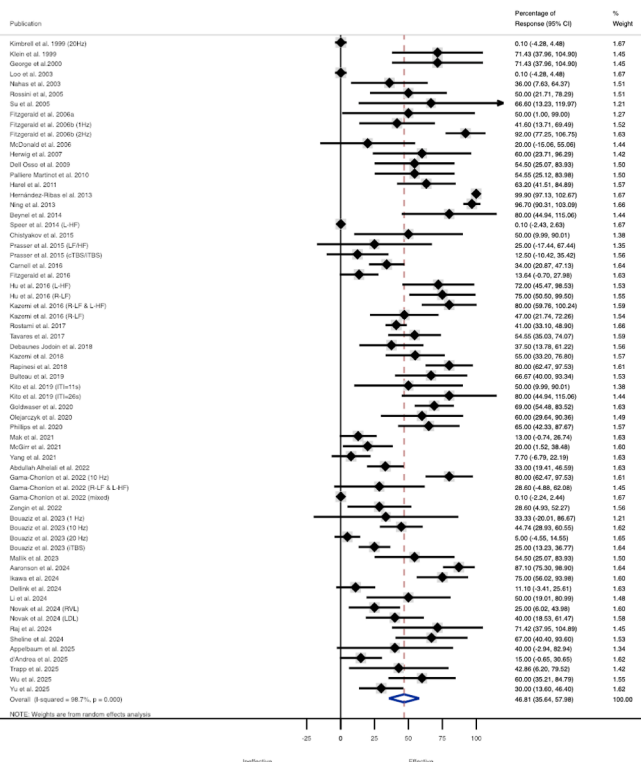
A

TMS in Bipolar Depression: Depression symptoms improvement in active TMS



B

TMS in Bipolar Depression: Response rate in active TMS



C

TMS in Bipolar Depression: Remission rate in active TMS

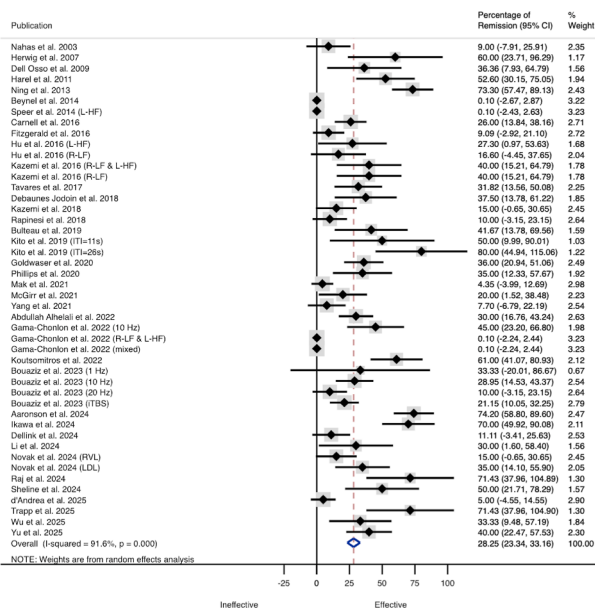


Figure 3. Forest plots of random-effects meta-analyses. There is a significant improvement in depression symptoms with active transcranial magnetic stimulation (TMS) (A). Mean rates of response and remission were 46.81% (B) and 28.25% (C), respectively.

Table 2. Subgroup Meta-Analysis for Different TMS Protocols

TMS Protocols		Response Rate			Remission Rate			Depression Improvement		
		<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	<i>d</i>	<i>p</i>
Left	iTBS-L	8	50.18	<.001	7	30.02	.011	8	1.84	<.001
	HF-rTMS-L	24	48.02	<.001	20	35.88	<.001	18	1.17	<.001
Right	HF-rTMS-R	1	25.00	.010	1	15.00	.060	1	1.86	<.001
	LF-rTMS-R	10	61.15	<.001	7	39.26	.004	6	2.46	<.001
	cTBS-R	3	35.6	.032	1	11.11	.134	2	0.87	<.001
Bilateral	HF-rTMS-BL	2	39.58	.322	1	10.00	.136	1	3.45	<.001
	LF-rTMS-R followed by HF-rTMS-L	5	45.06	.004	3	18.10	.018	2	1.23	.044
	cTBS-R followed by iTBS-L	1	12.50	.285	NA	NA	NA	NA	NA	NA
CBM-iTBS		1	42.86	.022	1	71.43	<.001	1	1.06	.024

BL, bilateral; CBM, cerebellar vermis; cTBS, continuous theta burst stimulation; HF, high-frequency; iTBS, intermittent theta burst stimulation; L, left; LF, low-frequency; NA, not applicable; R, right; rTMS, repetitive transcranial magnetic stimulation.

that TMS is well tolerated in BDep. The most common side effects were mild and transient, with a single uncomplicated generalized seizure reported in one article, and treatment-emergent mania/hypomania found at similar rates in active and sham study arms. These findings are consistent with existing evidence highlighting an excellent safety profile for rTMS, with extremely low rates of TMS-induced seizures or other severe side effects, and mostly mild side effects being reported (87–89). This is a clinically relevant finding since antidepressant treatments for BD are associated with increased risk of treatment-emergent mood switches, especially when used without appropriate mood stabilization, as has been shown for both electroconvulsive therapy and medication (90,91). Here, we found that the rate of treatment-emergent affective switches with TMS remained very low, consistent with previous research that has not identified an increased risk with active rTMS compared with sham stimulation (92).

Importantly, reporting of this potential side effect was inconsistent and often lacked clarity, as did the detailed characterization of bipolar subtypes (type I vs. type II), information that is clinically relevant for interpreting mood-switch risk across such subpopulations. Future studies of TMS in BDep should address this gap by systematically reporting safety outcomes and providing more comprehensive descriptions of patient characteristics.

Although previous work had already suggested that rTMS is efficacious (16,17,93), our work extends beyond available systematic reviews and meta-analyses. In addition to confirming that rTMS is useful and safe for clinical management of BDep in the largest pool of studies and patients to date, we also explored, for the first time, potential predictors of antidepressant effect that may guide current clinical work and future research, similar to what has been performed for other psychiatric conditions (94). First, regarding the characteristics

Table 3. Meta-Regression for Continuous Variables

Continuous Variables	Response Rate			Remission Rate			Depression Improvement		
	$\beta \pm SE$	<i>p</i>	<i>n</i>	$\beta \pm SE$	<i>p</i>	<i>n</i>	$\beta \pm SE$	<i>p</i>	<i>n</i>
Demographic									
Mean Age, Years	−0.73 ± 0.52	.164	46	−0.34 ± 0.45	.46	39	−0.03 ± 0.02	.111	40
Sex, % Female	0.00 ± 0.30	.999	42	−0.2 ± 0.35	.56	36	0.00 ± 0.01	.501	39
Clinical									
BDI, %	−0.045 ± 0.29	.875	19	−0.09 ± 0.24	.721	14	0.00 ± 0.01	.899	16
Depression Episode Duration, Months	0.20 ± 1.29	.879	14	−0.75 ± 1.13	.524	12	0.01 ± 0.05	.788	15
Number of Previous Depression Episodes	−4.11 ± 2.47	.140	9	0.76 ± 2.72	.789	8	−0.22 ± 0.14	.163	9
BD Duration, Years	−0.79 ± 1.12	.488	19	−1.99 ± 0.96	.054	18	−0.05 ± 0.06	.387	16
Depression Severity ^a	3.39 ± 2.42	.169	44	−2.68 ± 2.16	.233	39	0.23 ± 0.07	.003	46
TMS									
Number of Sessions	0.61 ± 0.38	.113	59	0.72 ± 0.39	.074	40	0.04 ± 0.02	.017	40
Number of Trains	0.12 ± 0.11	.267	37	0.15 ± 0.97	.13	26	0.00 ± 0.00	.44	25
Intertrain Interval	0.00 ± 0.04	.922	41	−0.45 ± 0.28	.11	30	−0.02 ± 0.01	.062	29
Pulses/Session	0.00 ± 0.00	.305	56	0.00 ± 0.00	.934	39	0.00 ± 0.00	.908	38
Stimulation Intensity	0.07 ± 0.28	.25	55	0.14 ± 0.26	.589	39	−0.16 ± 0.11	.17	38
Study Characteristics									
Study Quality	−8.87 ± 8.36	.293	65	−16.08 ± 7.11	.029	46	0.96 ± 0.29	.742	46

BDI, bipolar I disorder; TMS, transcranial magnetic stimulation.

^aSeverity assessed with baseline depression rating scale normalized to SD to make the studies comparable.

Table 4. Meta-Regression for Dichotomous Variables

Dichotomous Variables ^a	Response Rate			Remission Rate			Depression Improvement		
	$\beta \pm SE$	<i>p</i>	<i>n</i>	$\beta \pm SE$	<i>p</i>	<i>n</i>	$\beta \pm SE$	<i>p</i>	<i>n</i>
Clinical									
TRD Inclusion, <u>Yes</u> vs. No	-5.71 $\pm$ 8.5	.506	50	-7.27 $\pm$ 7.14	.316	35	-0.02 $\pm$ 0.35	.96	37
Use of Mood Stabilizers, <u>Yes</u> vs. No	6.68 $\pm$ 9.21	.471	65	-3.03 $\pm$ 8.86	.734	46	-0.16 $\pm$ 0.35	.65	46
TMS									
MT Determination, <u>EMG</u> vs. Visual	-11.74 $\pm$ 8.97	.198	43	-11.42 $\pm$ 8.05	.168	29	0.38 $\pm$ 0.26	.157	30
Accelerated Protocol, <u>Yes</u> vs. No	-5.39 $\pm$ 9.09	.555	61	-3.49 $\pm$ 8.62	.687	43	-0.10 $\pm$ 0.34	.757	42
Use of Neuronavigation, <u>Yes</u> vs. No	-7.79 $\pm$ 8.61	.370	55	-6.63 $\pm$ 7.78	.400	37	0.31 $\pm$ 0.29	.283	35
Frequency, <u>HF</u> vs. LF ^b	-14.72 $\pm$ 10.55	.170	47	-5.73 $\pm$ 10.23	.579	37	-0.92 $\pm$ 0.47	.058	35
Laterality, <u>BL</u> vs. UL	-12.28 $\pm$ 10.68	.255	59	-19.36 $\pm$ 10.19	.065	42	0.27 $\pm$ 0.54	.622	40
Side, <u>Left</u> vs. Right	-4.71 $\pm$ 9.16	.609	50	0.55 $\pm$ 9.13	.953	37	-0.50 $\pm$ 0.38	.196	36
<u>Left-rTMS</u> vs. Left-iTBS	3.02 $\pm$ 12.01	.804	34	-5.51 $\pm$ 10.05	.588	27	0.52 $\pm$ 0.35	.150	26
Study Characteristics									
Study Type, <u>RCT</u> vs. Non-RCT	-6.26 $\pm$ 7.2	.388	65	-7.78 $\pm$ 6.98	.272	46	0.19 $\pm$ 0.28	.51	46

BL, bilateral; EMG, electromyography; HF, high frequency; iTBS, intermittent theta burst stimulation; LF, low frequency; MT, motor threshold; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression; UL, unilateral.

^aEach variable was coded as 1 and 0; coefficients represent the effect of being in level 1 (underlined) compared with level 0.

^bVariable was categorized into 2 levels (LF: <5 Hz; HF: >5 Hz); a single 5-Hz study (*n* = 1) was excluded from frequency analysis because there is no clear consensus on frequency level classification and modulatory effects of such protocols (20).

of the treated population, studies including patients with more severe depressive symptoms at baseline were associated with better TMS antidepressant effects. While this finding is not surprising, because patients with the most severe symptoms have more room for measurable improvement (86), this has not been consistently reported in unipolar depression, for which severity has been considered both a negative and a positive predictor of TMS effect (95). Regarding treatment resistance, while this is a negative predictor of response to rTMS in unipolar depression (96), we did not find equivalent evidence for BDep, where studies that included patients with TRD demonstrated an antidepressant effect similar to those of studies that excluded this population. If confirmed, these differences reinforce important clinical distinctions between bipolar and unipolar depression (97), further suggesting that in BD, mood stabilization circuits are distinct from those affected in MDD (24,98,99). On the other hand, similar to MDD (95), there was a trend toward an association between longer illness duration and worse treatment outcomes, highlighting the importance of early accurate diagnosis and decisive treatment for all patients presenting with depressive symptoms (100). In future research, further attention should be devoted to the role of depression severity, as well as illness chronicity, as predictors of response to TMS in BDep. The use of psychotropic medications alongside TMS may influence its effectiveness in treating depression. While evidence remains limited (101), previous studies have suggested that anticonvulsant mood stabilizers (e.g., valproate, lamotrigine) could impact the therapeutic response to TMS by modifying neuroplasticity (102). On the other hand, lithium has not been consistently associated with reduced rTMS efficacy (101). Our meta-regression analysis showed no differences in overall depression improvement or response and remission rates in studies including patients taking any mood stabilizer.

Within the description of study-level predictors of antidepressant effectiveness, our work is of further value for

practicing TMS physicians, because it provides guidance on the most effective protocols for BDep (103). We found that both left-sided HF-rTMS and right-sided LF-rTMS were robustly and significantly associated with clinical antidepressant effects across the different outcomes, as in unipolar depression (7). Importantly, for the first time and contrary to negative results in previous studies on the treatment of BDep (15), we found that iTBS protocols targeting the left DLPFC were similarly effective to HF-rTMS applied to the same target, consistent with what has been reported for unipolar depression (85). Furthermore, regarding other parameters of antidepressant effectiveness of TMS protocols for BDep, we found that an increased number of sessions was associated with better outcomes, as had already been shown in older adults treated with TMS for depression (104). However, effectiveness did not depend on the number of pulses or trains per session, intertrain interval, stimulation intensity, or method of determining motor threshold, target method, use of accelerated protocols, frequency, or laterality and side of stimulation. Future work would benefit from determining, within restricted parameter space, the optimal rTMS parameters for BDep, including the comparison of HF-rTMS with iTBS.

The interpretation and application of our findings should consider the limitations of this work. First, 28 studies reported mixed samples, consisting of patients diagnosed with BDep or unipolar depression, and thus potential selection bias of the participants with BDep cannot be fully excluded. Second, additional information, such as demographics, psychiatric history, and disease characteristics were not consistently reported in the analyzed studies. This limited the inclusion of such variables in the meta-regressions and subgroup meta-analysis, potentially restricting our ability to explore the impact of TMS in subdomains of symptoms in BDep, for example, sleep (105,106). According to best practices, we have only performed such analyses when sufficient studies were available to draw meaningful conclusions (20). Additionally, not all trials reported remission outcomes, limiting their inclusion in the respective

meta-analysis. Some key outcomes could not be obtained despite our efforts to contact study authors to provide missing data, with success in several cases. Third, selected studies applied a variety of TMS protocols, resulting in high heterogeneity across studies. Such heterogeneity of TMS protocols is likely to be related to the relative novelty of TMS as a therapeutic approach for BDep treatment, and as the field continues to mature, the most appropriate stimulation parameters are expected to be further clarified. Here, we used meta-regression and subgroup meta-analysis to contribute toward this clarification (20). Another source of heterogeneity results from different outcome measures being used across studies. To mitigate this limitation, we used standardized effect sizes as well as random-effects meta-analysis, minimizing the potential impact of these differences. Finally, the possibility of publication bias cannot be excluded, and examination of trial registrations reveals numerous potentially unpublished trials, including industry-sponsored trials (for example, [NCT01566591](#)). However, it is noteworthy that Trim-Fill Duval-Tweedie test suggests an increased OR for response and remission in BDep when including potentially omitted studies, increasing confidence in our results regarding efficacy. Fourth, our meta-regression analyses are not based on individual patient data but rather on study-level averages, making them susceptible to ecological fallacy. Thus, these associations may not reflect individual-level effects, warranting confirmation through, for example, patient-level meta-analyses or prospective studies to validate and strengthen our findings. Finally, we acknowledge that performing multiple exploratory tests may increase the risk of false positive results. While we did not apply a formal correction for multiple comparisons, the use of standardized methods and procedures for meta-analytic research helps to mitigate this risk. In fact, meta-analyses are typically conducted to clarify potential false positives from individual studies and may not require formal correction but rather careful interpretation of the results (20,107).

Conclusions

We showed that rTMS was associated with a significant antidepressant effect relative to sham, as well as a very large therapeutic effect. Most importantly, the rates of clinical response and remission parallel those reported in unipolar depression, and this treatment is also well tolerated in BDep as in MDD. Our results extend beyond previous literature since we have found potential determinants of such a therapeutic effect. We showed that illness severity and increased number of sessions predicted greater antidepressant effects in BDep, while longer illness duration seemed to predict a lower likelihood of symptom remission, at a trend level. Finally, we help guide clinicians practicing TMS by showing that HF and LF protocols on the left and right DLPFC, respectively, are robustly associated with positive outcomes as in unipolar depression. Most importantly, for the first time, we showed that iTBS of the left DLPFC is not inferior to more widely used HF-rTMS protocols, and is therefore an option that should be further studied and used in clinical practice.

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