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RESEARCH ARTICLE

Repetitive transcranial magnetic stimulation for generalized anxiety and panic disorders: A systematic review and meta-analysis

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BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved, noninvasive modality for treating major depressive disorder and obsessive-compulsive disorder. Earlier studies evaluating therapeutic effects of rTMS on symptom scores of patients with generalized anxiety disorder (GAD) and panic disorder (PD) have yielded inconsistent findings.

METHODS: We performed a systematic review and meta-analysis of interventional studies assessing the effect of rTMS on symptom scores in patients with GAD or PD with or without psychiatric comorbidities using studies published up to April 2021. We used DerSimonian-Laird random effects models to obtain pooled standardized mean difference (SMD) and 95% CI.

RESULTS: A total of 13 studies consisting of 677 participants (404 treated with rTMS and 273 without rTMS) were included in this meta-analysis. In GAD patients with or without any comorbidities, rTMS therapy demonstrated significant improvements in anxiety (SMD = 1.45; $P < .001$) and depression (SMD = 1.65; $P < .001$) scores regardless of rTMS parameters. Overall anxiety (SMD = 0.24; $P = .48$) and panic severity (SMD = 1.19; $P = .054$) scores did not significantly improve after rTMS therapy in patients with PD.

CONCLUSIONS: rTMS is safe and improves anxiety and depression scores only in GAD patients, regardless of underlying comorbidities or rTMS parameters.

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INTRODUCTION

Anxiety disorder is the most prevalent psychiatric disorder, with a 12-month prevalence of 11.6% globally[1] and 21.3% in the United States.[2] Generalized anxiety disorder (GAD) and panic disorder (PD) are the most common chronic anxiety disorders and often coexist with other anxiety or psychiatric disorders.[3] Although the mechanistic relationship between PD and GAD is unclear, they primarily differ based on physical, behavioral, and psychological experiences. PD is characterized by sudden, spontaneous, and recurrent episodes of intense fear and worry, while GAD patients experience prolonged, persistent, and excessive anxiety. These disorders appear to demonstrate pathophysiological changes and functional changes in brain regions.[4-6] GAD and PD are associated with disability, psychosocial decline, poor quality of life, and economic burden.[7,8] Anxiety disorders often are treated with cognitive-behavioral therapy (CBT) and medications such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. However, 40% of patients do not respond to these interventions.[9] Treatment-resistant patients experience disability and poor quality of life. Although CBT shows improved response as a first-line treatment for anxiety disorders and has been modified for GAD[10,11] and PD,[12] many patients do not experience symptom improvement after CBT,[13,14] indicating the need for alternative effective treatment strategies for anxiety disorders. Alternative safe and effective treatment approaches for GAD and PD are required given their high prevalence with other psychiatric illnesses. One evidence-based option could be repetitive transcranial magnetic stimulation (rTMS) therapy.

rTMS is a noninvasive and safe neuromodulation technique that was FDA-approved to treat major depressive disorder (MDD) and obsessive-compulsive disorder in 2008 and 2018, respectively.[15] rTMS influences neuroplasticity by changing the efficiency of synapses by promoting or inhibiting their activation and can induce prolonged effects beyond the stimulation period. These properties have made rTMS a promising treatment option for neurologic and psychiatric disorders. Several meta-analyses established rTMS effectiveness among patients with posttraumatic stress disorder (PTSD).[16-18] Researchers have attempted to evaluate the effect of rTMS in patients with GAD and PD[4,19] because these disorders often coexist with MDD[3] and PTSD.[20] PD increases the likelihood of GAD,[21] and could overlap with symptoms and neural mechanisms. Recently, 2 review studies evaluated the use of rTMS among GAD or PD patients. A review[15] based on 17 studies that included trauma disorders (11 studies), GAD (4 studies), and PD (2 studies) did not evaluate efficacy of rTMS in terms of any rTMS parameters because of limited studies on GAD and PD patients. Another review of GAD patients[22] included mostly Chinese studies (90%). Although the effectiveness of rTMS has been established in patients with PTSD and MDD, the role of rTMS for treating GAD and PD is unclear.

We investigated the effect of rTMS on symptom scores in patients diagnosed with GAD and PD with or without psychiatric comorbidities separately by performing an updated systematic review and meta-analysis. We also examined the effect of rTMS on symptom scores according to rTMS parameters (stimulation site with sidedness, percentage of resting motor threshold [RMT], pulse frequency, and number of sessions).

METHODS

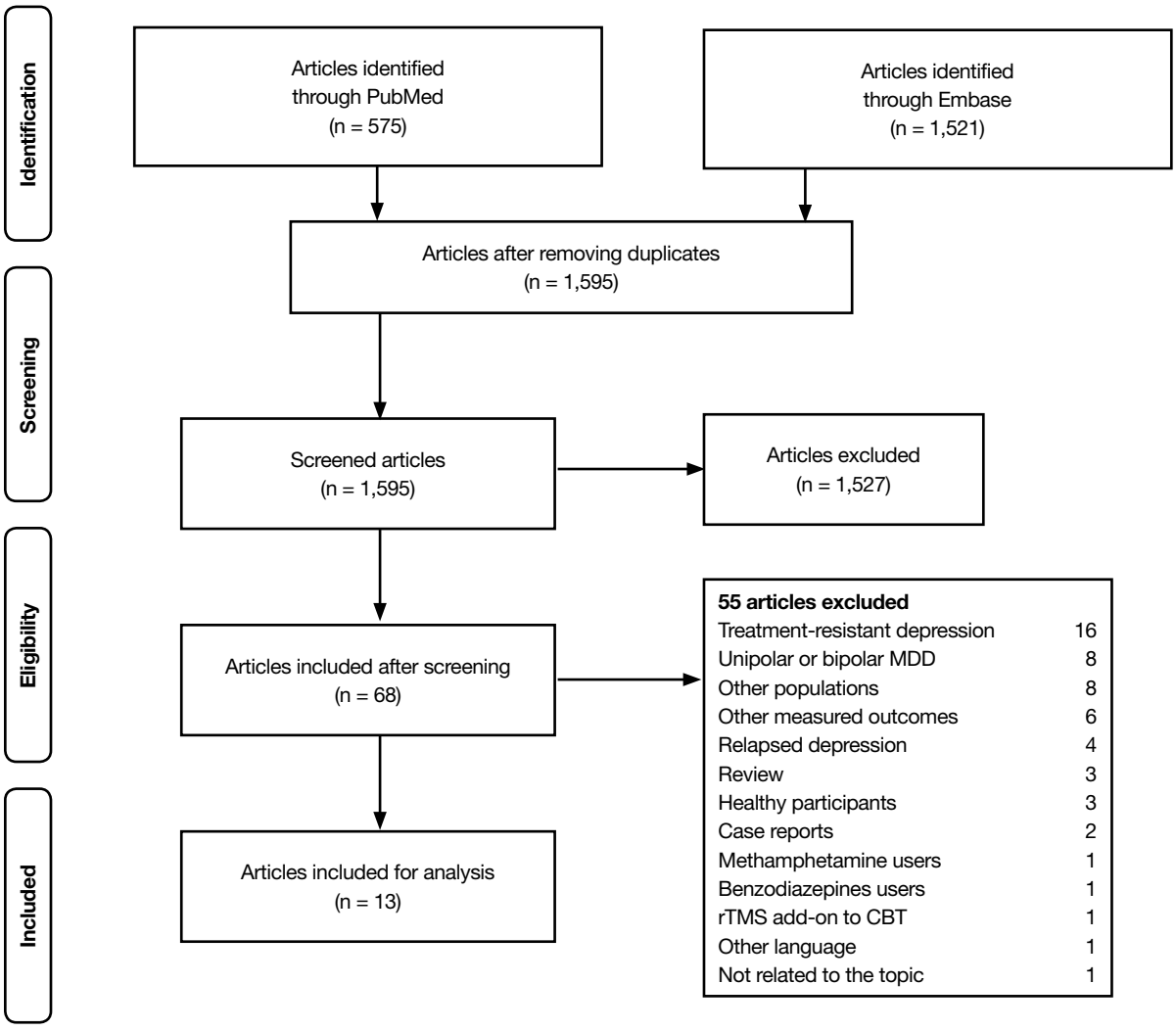
Data source and study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Statistical Analyses and Methods in Biomedical Research (SAMBR)[23,24] guidelines for performing and reporting the results of this study. We conducted an electronic literature search in PubMed and Embase for articles published up to April 2021. Keywords used for the literature search included "(transcranial magnetic stimulation OR TMS OR repetitive transcranial magnetic stimulation) AND (anxiety OR generalized anxiety disorder OR panic disorder)." We also reviewed reference lists of included articles to include any articles missed by the initial search.

Inclusion and exclusion criteria

Studies were included in accordance with PICOS (Participants, Interventions, Comparison, Outcomes, and Study Design) with the following inclusion criteria: (1) participants had a diagnosis of GAD or PD according to the Mini International Neuropsychiatric Interview, DSM-IV, International Classification of Diseases, or the third edition of the Chinese Mental Illness Diagnostic Standard; (2) intervention arm included rTMS therapy with or without pharmacotherapy; (3) comparison arm included before the rTMS intervention (participant's

FIGURE 1
Flow chart for study selection



CBT: cognitive-behavioral therapy; MDD: major depressive disorder; rTMS: repetitive transcranial magnetic stimulation.

own control) or a parallel control group with sham rTMS or without rTMS; (4) the primary outcomes included changes in anxiety symptoms measured using the Hamilton Anxiety Rating Scale (HAM-A) and depression scores measured using the Hamilton Depression Rating Scale in GAD and PD patients, while panic severity symptoms were measured using the Panic Disorder Severity Scale in PD patients and the secondary outcome evaluated the safety of rTMS therapy; and (5) study design included any intervention studies, either uncontrolled or controlled trials, including randomized controlled trials (RCT) and non-RCTs. Any article not written in English was excluded from this study. Abstracts or studies such as case reports, animal studies, pilot studies, meta-analysis, systematic reviews, and narrative reviews were excluded.

Methodological quality assessment

The Methodological Index for Non-Randomized Studies (MINORS) scale was used to appraise the quality of uncontrolled and controlled studies.[25] This scale is based on 12 items: the first 8 are used for uncontrolled studies, and an additional 4 are used for controlled studies. A score from 0 to 2 was given for all items according to

whether the item-related attributes was reported or not, as well as adequate or not (0 [unreported], 1 [reported but inadequate], or 2 [reported and adequate]). The maximum scores for uncontrolled and controlled studies according to MINORS were 16 and 24, respectively.

Data extraction

Two authors (JC and BT) independently performed the search, assessed eligibility criteria, reviewed each article, and extracted data related to this study. Any disagreement was resolved by discussion with a senior author (AD). We collected the study, patient, and rTMS characteristics involving the first author of the study; year of publication; study type/design (pre-post or rTMS vs no rTMS); country; sample size in the rTMS and non-rTMS groups; type of controlled study (RCT or non-RCT); patient characteristics such as age (years) and sex (percent female); type of anxiety disorder (GAD or PD); instruments used for anxiety, depression, and panic severity assessments; diagnostic criteria; rTMS parameters such as stimulation site with sidedness, pulse frequency, percent of RMT, number of rTMS sessions, and number of pulses per session; and mean and standard deviation of pre- and post-measures of anxiety, depression, and panic severity in rTMS and non-rTMS groups from the eligible studies.

Statistical analysis

STATA 15.1 was used for data management and statistical analysis. GAD and PD studies were analyzed separately. Outcomes in the study were improvements in anxiety, depression, and panic severity scores measured using validated instruments. In pre-post studies with the rTMS group only, we computed a standardized mean difference (SMD) of pre- and post-rTMS scores for each outcome and its standard error by Hedges method for each study. In controlled studies reporting pre- and postscores in rTMS and non-rTMS groups separately, we computed mean differences of scores before and after intervention in each active rTMS and no rTMS group, and then a SMD of the mean changes between groups and its standard error by the Hedges method for each score in each study was computed.[15] The SMDs of pre- and postscores in the rTMS group only and mean differences in pre- and postscores between rTMS and non-rTMS groups were combined across the studies using the DerSimonian-Laird random effects model and estimated the pooled SMD and a 95% CI. Baseline SD was used for computing the standard error of the mean difference. Significantly positive SMD indicates improvement in outcome measure in the rTMS group compared with baseline control or non-rTMS group. An I^2 statistic was computed to assess the heterogeneity in effect sizes across the studies.[26] An I^2 >70% indicated a significant presence of heterogeneity across the studies. Publication bias was evaluated using Egger's test. Various sensitivity and subgroup analyses according to study characteristics and rTMS parameters—such as rTMS frequency (low pulse frequency: <10 Hz vs high pulse frequency: ≥10 Hz), RMT (low ≤100% vs high >100%), number of rTMS sessions (low: ≤10 vs high: >10), intervention duration (short: ≤3 weeks vs long: >3 weeks), stimulation site with sidedness (right dorsolateral prefrontal cortex [DLPFC], left DLPFC, and bilateral), control group (uncontrolled vs controlled), study type (non-RCT vs RCT), comorbidity (absence or presence), and sample size (≤30 vs >30)—were performed to evaluate the possible reasons for heterogeneity in estimates and factors associated with effect of rTMS therapy.

RESULTS

Study selection

Using the specified search criteria, we obtained 2,096 articles (PubMed: 575 and Embase: 1,521). After employing the eligibility criteria, 13 published articles[27-39] with 14 study datasets met inclusion criteria for a systematic review. **FIGURE 1** displays the selection of eligible articles at each step of the screening process. Of 14 studies, 8 were based on GAD patients and 6 studies evaluated PD patients. Among 8 GAD studies, 3 included GAD patients with psychiatric comorbidity (1 study with insomnia, 1 study with MDD, and 1 study with multiple comorbidities). Among 6 PD studies, 4 included PD patients with comorbidity (all studies with only MDD). The average therapy duration was 4.25 weeks (median 5, range 1 to 6) in GAD studies and 3.5 weeks (median 3.5, range 2 to 6) in PD studies. The details of study characteristics and rTMS parameters of included studies are shown in **TABLE 1**.

Qualitative synthesis of studies

Among 8 GAD studies, 7 studies[28,30,33-35,38,39] reported depression and anxiety scores. All the GAD studies demonstrated significant improvements in anxiety and

TABLE 1
Summary of study characteristics

Study	Country	Anxiety disorder	Diagnostic criteria	Comorbidities	Study type	Outcome assessment	Treatment duration (weeks)	Comparison
Huang et al[35] (2018)	China	GAD	DSM-IV	GAD with insomnia	RCT	HAM-A HAM-D	1	rTMS vs sham control
Lu et al[37] (2018)	China	GAD	CCMD-3	GAD alone	Uncontrolled	HAM-A	2	Pre-post
Dilvok et al[34] (2017)	Bulgaria; Canada	GAD	MINI	GAD alone	RCT	HAM-A HAM-D	6	rTMS vs sham control
Diefenbach et al[33] (2016)	USA	GAD	MINI	GAD alone	RCT	HAM-A HAM-D	6	rTMS vs sham control
Bystritsky et al[30] (2008)	USA	GAD	MINI	GAD alone	Uncontrolled	HAM-A HAM-D	3	Pre-post
Zhang et al[39] (2019)	China	GAD	DSM-IV	GAD with multiple comorbidities	Uncontrolled	HAM-A HAM-D	4	Pre-post
Clarke et al[38] (2019)	Australia	GAD	MINI	GAD with MDD	Non-RCT	HAM-A HAM-D	6	Depressed patients with GAD vs depressed patients only
White et al[28] (2015)	USA	GAD	DSM-IV	GAD alone	Uncontrolled	GAD-7 HAM-D	5 to 6	Pre-post
Clarke et al[38] (2019)	Australia	PD	MINI	PD with MDD	Non-RCT	HAM-A HAM-D	6	Depressed patients with PD and agoraphobia vs depressed patients only
Prasko et al[29] (2007)	Czech Republic	PD	ICD-10	PD alone	RCT	HAM-A PDSS	2	rTMS vs sham control
Mantovani et al[31] (2013)	USA	PD	DSM-IV	PD with MDD	RCT	HAM-A PDSS HAM-D	4	rTMS vs sham control
Kumar et al[36] (2018)	India	PD	ICD-10	PD with MDD	Uncontrolled	PDSS HAM-D	4	Pre-post
Mantovani et al[27] (2007)	USA	PD	DSM-IV	PD with MDD	Uncontrolled	HAM-A PDSS HAM-D	2	Pre-post
Depperman et al[32] (2014)	Germany	PD	DSM-IV	PD alone	RCT	HAM-A PDSS	3	rTMS vs sham control

[a]n1: sample size for rTMS group; n2: sample size for control group.

CCMD-3: Chinese Mental Illness Diagnostic Standard, 3rd edition; GAD: generalized anxiety disorder; GAD-7: generalized anxiety disorder 7-item scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; ICD-10: International Classification of Diseases, 10th revision; LDLPFC: left dorsolateral prefrontal cortex; MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; NR: not reported; PD: panic disorder; PDSS: panic disorder severity scale; PPS: pulses per session; RCT: randomized controlled trial; RDLPFC: right dorsolateral prefrontal cortex; rTMS: repetitive transcranial magnetic stimulation.

depression scores after rTMS. Among 6 PD studies, only 2 studies[27,31] assessed all outcome scores. In addition, 2 of 3 PD studies reported anxiety[29,32] and 1 reported depression[36] scores with panic severity scores. Only 1 study[38] reported anxiety and depression scores without panic severity scores. None of the PD studies showed statistically significant improvement in anxiety scores after rTMS compared with either baseline control or non-rTMS group except for 1 study.[27] Only 2 uncontrolled PD with MDD studies[27,36] yielded improvements in panic severity and depression scores, while 1 controlled PD with MDD study[31] produced improvement in panic severity scores only. All 14 studies showed improvement in reported outcome measures in the rTMS group (**FIGURE 2**). Among the reported adverse events, headache was most common, followed by pain at the stimulation site or scalp pain or discomfort, and neck pain. However, there was no difference in adverse events between rTMS

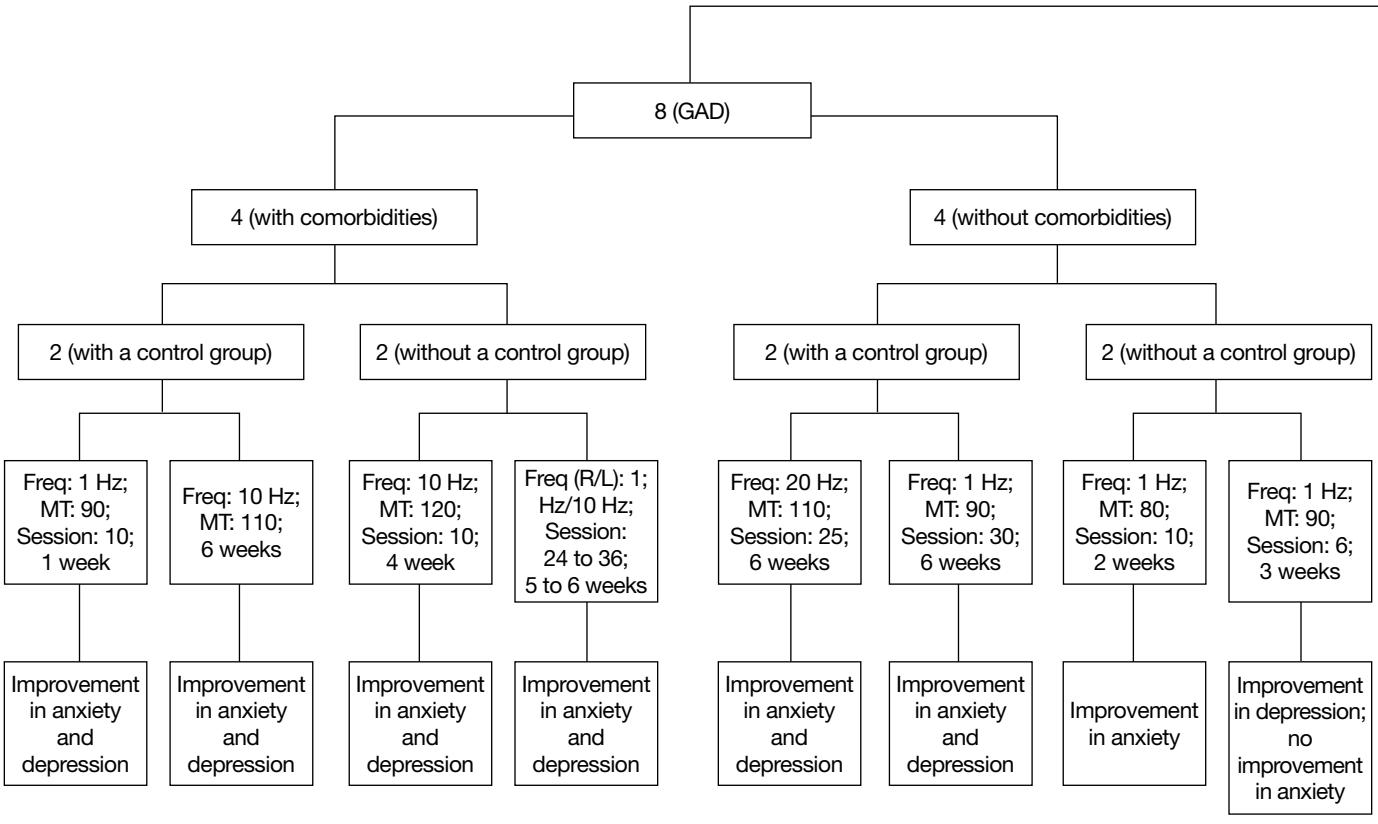
	Age, mean (SD or range)	Sex, female/male	n1/n2[a]	rTMS parameters				
				Stimulation site	Frequency	Motor threshold	Number of sessions	PPS
	rTMS: 44.9 (11.6) Control: 45.2 (10.8)	18/18	18/18	Right parietal lobe	1 Hz	90%	10	1,500
	45.5 (12.7)	17/11	28	RDLPFC LDLPFC	1 Hz 1 Hz	80%	10	1,500 750
	rTMS: 34 (7) Control: 38 (10)	19/21	15/25	RDLPFC	20 Hz	110%	25	3,600
	rTMS: 44 (11.9) Control: 44.6 (14.7)	19/6	13/12	RDLPFC	1 Hz	90%	30	900
	45.3 (12.1)	5/5	10	RDLPFC	1 Hz	90%	6	150
	43.7 (26.4)	68/49	117	LDLPFC	10 Hz	120%	10	2,400
	rTMS: 48.2 (14.3) Control: 50.8 (15.8)	107/71	102/76	LDLPFC RDLPFC	10 Hz	110%	NR	NR
	42.5 (NR)	8/5	13	RDLPFC LDLPFC	1 Hz 10 Hz	NR	24 to 36	NR
	50.8 (12.3)	74/43	41/76	LDLPFC RDLPFC	10 Hz	110%	NR	NR
	rTMS: 33.7 (9.2) Control: 33.8 (12.2)	11/4	7/8	RDLPFC	1 Hz	110%	10	1,800
	rTMS: 40.2 (10) Control: 39.8 (13.3)	13/12	12/13	RDLPFC	1 Hz	110%	20	1,800
	38.23 (6.52)	NR	13	NR	20 Hz	110%	20	NR
	NR	3/3	6	RDLPFC	1 Hz	100%	10	NR
	rTMS: 37.6 (19 to 63) Control: 36.3 (19 to 64)	41/26	22/45	LDLPFC	NR	80%	15	NR

and non-rTMS groups (**SUPPLEMENTAL TABLE 1,** available at www.aacp.com).

Characteristics of included studies for meta-analysis

Only 1 article[28] used an instrument other than the HAM-A to assess anxiety scores and was excluded from the meta-analysis (n = 13 studies). A total of 13 studies included 677 patients (404 treated with rTMS and 273 without rTMS); most participants were female (59.5%). Of 13 studies, GAD studies were based on 434 patients (303 treated with rTMS and 131 without rTMS) with 58% being female (253 of 434) while PD studies included 243 patients (101 treated with rTMS and 142 without rTMS) and 62% (142 of 230) were female. Sex information was missing for 1 PD study (**TABLE 1**). No differences in patient characteristics and rTMS parameters, including therapy duration, were observed between GAD and PD studies except

FIGURE 2
Qualitative analysis of rTMS therapy on outcome scores by GAD and PD patients



GAD: generalized anxiety disorder; MDD: major depressive disorder; MT: motor threshold; PD: panic disorder; rTMS: repetitive transcranial magnetic stimulation.

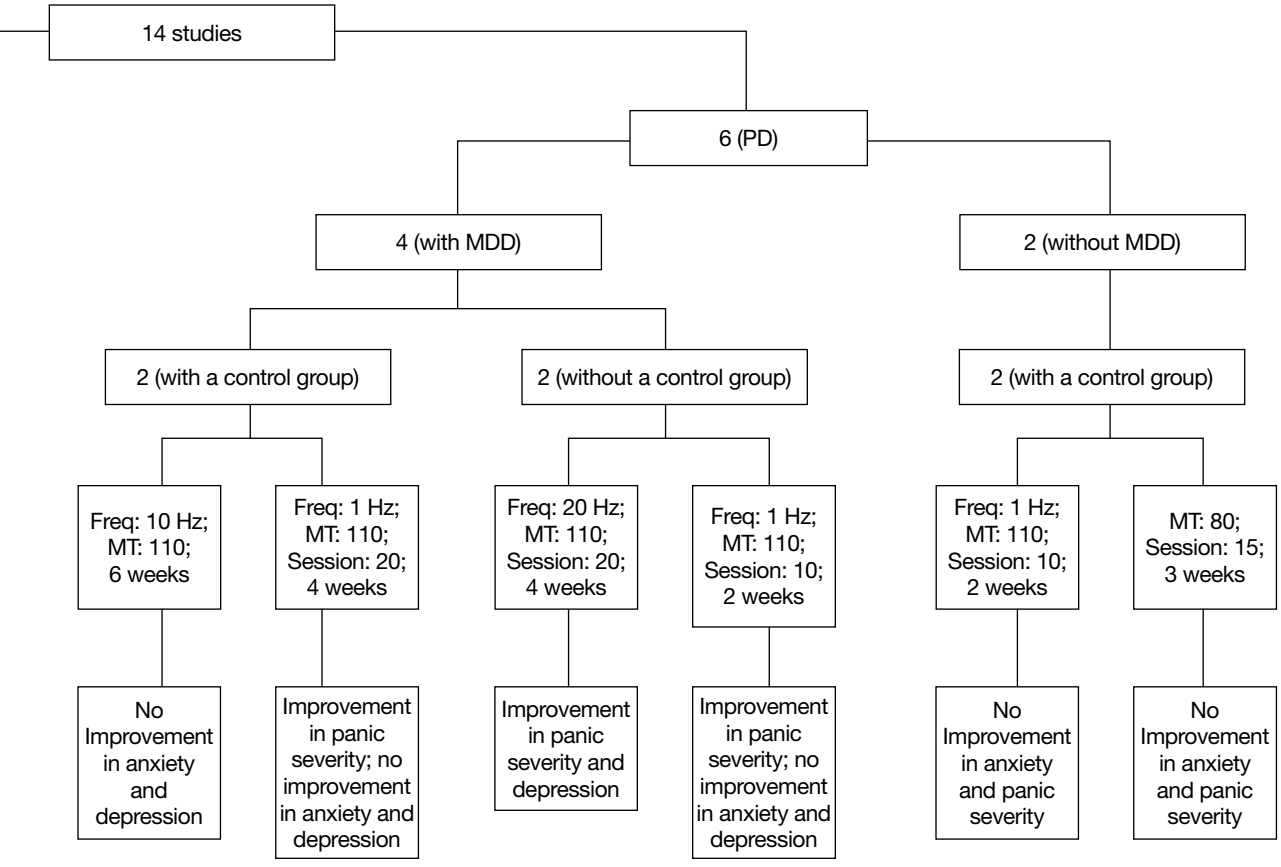
that the PD studies mostly included patients with MDD (**SUPPLEMENTAL TABLE 2,** available at www.aacp.com).

Quality of included studies

The results of the quality assessment for each study are shown in **SUPPLEMENTAL TABLE 3** (available at www.aacp.com). Most studies were evaluated as good quality. The publication bias assessed using Egger's test for each outcome in GAD and PD studies is reported in **SUPPLEMENTAL TABLE 4** (available at www.aacp.com). The nonsignificant *P* associated with regression coefficients indicate an absence of a small sample size effect for any outcome score.

Comparisons of outcome scores among GAD patients

In GAD patients, rTMS therapy significantly improved anxiety (SMD = 1.46; 95% CI, 0.86 to 2.05; $P < .001$; $I^2 = 87.9\%$) and depression (SMD = 1.65; 95% CI, 0.80 to 2.50; $P < .001$; $I^2 = 93\%$) scores with a significant presence of heterogeneity regardless of rTMS parameters (**TABLE 2** and **FIGURE 3**). **TABLE 2** shows effect sizes of rTMS on anxiety and depression scores according to study characteristics. In the heterogeneity assessments performed after removing 2 GAD studies with MDD patients,[38,39] heterogeneity was completely eliminated for estimating the effect size for anxiety outcome (SMD = 1.67; $P < .001$; $I^2 = 0.0\%$). Similarly, heterogeneity was reduced for estimating the rTMS effect on depression outcome (SMD = 1.23; $P < .001$, $I^2 = 39.5\%$) after excluding 2 studies with MDD patients[38,39] and a study that used rTMS at the highest pulse frequency compared with other studies.[34] Improvement in anxiety scores remained significant in GAD patients with (SMD = 1.28; $P = .014$) or without (SMD = 1.57; $P < .001$) comorbidities. However, GAD patients without comorbidities (SMD = 2.39; $P = .008$)



showed a greater improvement in depression scores compared with GAD patients with comorbidities (SMD = 1.07; $P = .041$). Uncontrolled studies yielded a marked improvement in anxiety scores (SMD = 1.61; $P < .001$) compared with controlled studies (SMD = 1.24; $P = .006$). However, the effect size for depression score remained similar in uncontrolled and controlled studies. RCT studies yielded marked improvements in both outcome scores compared with non-RCT studies (**TABLE 2**).

Studies that included rTMS intervention with low pulse frequency (<10 Hz), low RMT (≤100%), over the right DLPFC with a relatively lower number of rTMS sessions, and shorter treatment duration demonstrated greater improvements in anxiety scores without a significant heterogeneity. However, rTMS with high pulse frequency (≥10 Hz), high RMT (>100%) over the right DLPFC in studies with a higher number of rTMS sessions (>10), and longer treatment duration (>3 weeks) showed improvements in depression scores of GAD patients. rTMS on bilateral stimulation sites yielded the least improvement in outcome scores (**SUPPLEMENTAL TABLE 5,** available at www.aacp.com).

Comparison of outcome scores among PD patients

Among PD patients, there was no improvement observed in anxiety scores after rTMS (SMD = 0.24; $P = .48$; $I^2 = 73.5\%$) (**TABLE 3** and **FIGURE 4**). After removing 1 small uncontrolled study,[27] we further observed no improvement in anxiety scores even with a substantial reduction in heterogeneity in treatment effect (SMD = 0.03; $P = .89$; $I^2 = 45.3\%$). Although improvement in panic severity scores after rTMS was noted, the result did not reach statistical significance (SMD = 1.19; 95% CI, –0.02 to 2.40; $P = .054$; $I^2 = 86.9\%$).

TABLE 2
The effect of rTMS on outcome scores by study characteristics in generalized anxiety disorder patients

	Anxiety				Depression			
Characteristics	**N**	**SMD (95% CI)**	***P***	***I²***	**N**	**SMD (95% CI)**	***P***	***I²***
Overall	7	1.45 (0.86 to 2.05)	<.001	87.9%	6	1.65 (0.80 to 2.50)	<.001	93.0%
Subpopulation	5[a]	1.67 (1.32 to 2.02)	<.001	0.0%	3[b]	1.23 (0.75 to 1.71)	<.001	0.0%
Study characteristics								
Comorbidities								
Absent	4	1.57 (1.18 to 1.96)	<.001	0.00%	3	2.39 (0.63 to 4.15)	.008	88.60%
Present	3	1.28 (0.26 to 2.31)	.014	95.10%	3	1.07 (0.04 to 2.1)	.041	95.30%
Study type								
Non-RCT	4	1.37 (0.52 to 2.22)	.002	93.00%	3	1.19 (0.09 to 2.3)	.034	95.30%
RCT	3	1.59 (1.08 to 2.09)	<.001	17.00%	3	2.23 (0.42 to 4.03)	.016	91.50%
Control group								
Present	4	1.24 (0.35 to 2.12)	.006	86.80%	4	1.71 (0.4 to 3.03)	.011	93.10%
Absent	3	1.61 (1.35 to 1.87)	<.001	0.00%	2	1.78 (1.49 to 2.08)	<.001	0.00%
Sample size								
≤30	3	1.7 (1.23 to 2.17)	<.001	0.00%	2	1.45 (0.78 to 2.12)	<.001	0.00%
>30	4	1.27 (0.45 to 2.1)	.002	92.80%	4	1.77 (0.64 to 2.9)	.002	95.80%

[a]After excluding 2 studies with MDD patients.
[b]After excluding 2 studies with MDD patients and 1 study with the highest pulse frequency.
MDD: major depressive disorder; RCT: randomized controlled trial; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

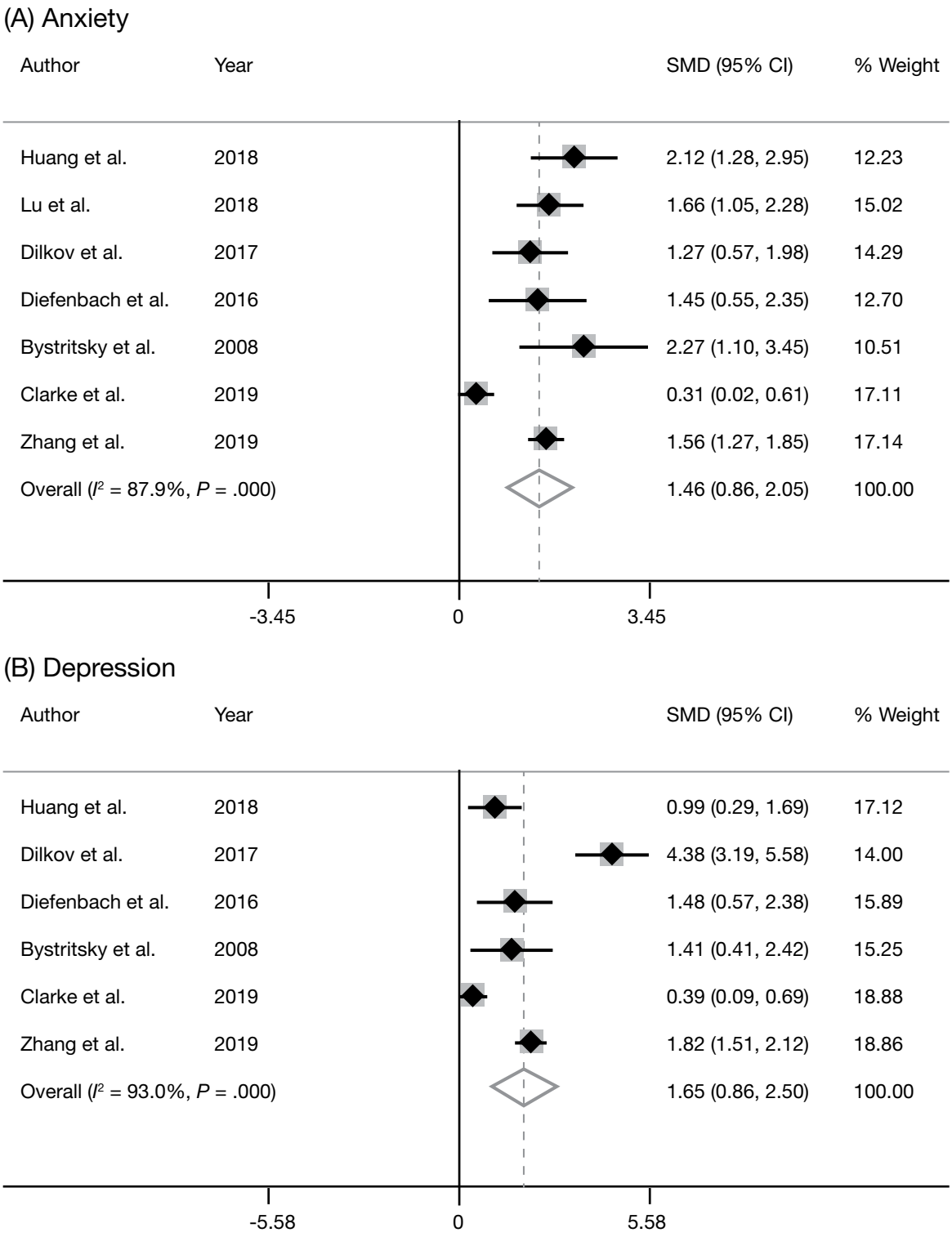
Restricting the analysis to studies of patients with PD and comorbid MDD produced an improvement in panic severity scores (SMD = 2.25; $P < .001$, $I^2 = 0\%$) without any heterogeneity. The effect of rTMS on panic severity scores remained the same for non-RCT studies (SMD = 2.23; $P < .001$; $I^2 = 0\%$) or uncontrolled studies (SMD = 2.23; $P < .001$, $I^2 = 0\%$) involving patients with PD and MDD. Patients treated with rTMS also demonstrated significant improvement in depression scores (SMD = 1.06; $P = .022$; $I^2 = 79.4\%$) with significant presence of heterogeneity. rTMS group had a favorable change in depression scores (SMD = 0.34; $P = .056$; $I^2 = 0\%$) without presence of heterogeneity after excluding 2 small studies.[27,36] The uncontrolled PD studies showed the greatest improvement in depression scores after rTMS without any heterogeneity (SMD = 2.06; $P < .001$; $I^2 = 0\%$) (**TABLE 3**).

None of the subgroup analyses based on rTMS parameters showed a beneficial treatment effect on all outcome scores in PD patients. However, studies of patients with PD and MDD with longer rTMS treatment duration (>3 weeks) yielded greater improvements in panic severity scores (SMD = 2.30; $P < .001$) compared with studies with shorter treatment duration (≤3 weeks) (**SUPPLEMENTAL TABLE 6,** available at www.aacp.com).

DISCUSSION

To our knowledge, this is the most comprehensive systematic review and meta-analysis study evaluating the safety and treatment effect of rTMS on symptom scores among GAD and PD patients with or without psychiatric comorbidities. This study confirms that rTMS improves symptoms of anxiety and depression in GAD patients with or without comorbidities regardless of rTMS parameters. Furthermore, the efficacy of rTMS was confirmed in GAD patients using an analysis of randomized trial studies only. rTMS did not show significant improvement in anxiety and panic severity scores for all PD patients. However, patients with PD and MDD treated with rTMS showed significant improvement in panic severity and depression scores but not anxiety scores. We did not

FIGURE 3
Effect of rTMS on anxiety and depression scores in GAD patients



GAD: generalized anxiety disorder; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

TABLE 3
The effect of rTMS on outcome scores by study characteristics in panic disorder patients

	Anxiety				Depression		
Characteristics	**N**	**SMD (95% CI)**	***P***	***I²***	**N**	**SMD (95% CI)**	***P***
Overall	5	0.24 (–0.42 to 0.91)	.48	73.5%	4	1.06 (0.15 to 1.97)	.022
Subpopulation	4[a]	0.03 (–0.41 to 0.47)	.89	45.30%	2[b]	0.34 (-0.01 to 0.68)	.056
Study characteristics							
Comorbidities							
Absent	2	-0.41 (-1.17 to 0.35)	.29	40.40%	NSD	NSD	NSD
Present	2	0.82 (-0.19 to 1.83)	.11	76.20%	4	1.06 (0.15 to 1.97)	.022
Study type							
Non-RCT	2	1.58 (-1.24 to 4.4)	.27	88.10%	3	1.44 (0.04 to 2.83)	.044
RCT	3	-0.15 (-0.77 to 0.47)	.63	44.70%	1	0.3 (-0.49 to 1.09)	.46
Control group							
Present	4	0.03 (-0.41 to 0.47)	.89	45.30%	2	0.34 (-0.01 to 0.68)	.056
Absent	1	3.19 (1.26 to 5.11)	.001	NSD	2	2.06 (1.24 to 2.89)	<.001
Sample size							
≤30	3	0.68 (-1.11 to 2.46)	.46	85.40%	3	1.45 (0.1 to 2.79)	.035
>30	2	0.14 (-0.25 to 0.54)	.47	26.40%	1	0.34 (-0.04 to 0.73)	.078

[a]After excluding 1 small uncontrolled study (with 6 patients).
[b]After excluding 2 small uncontrolled studies (with 6 patients and 13 patients).
[c]After excluding studies conducted on PD patients without comorbid MDD.

NSD: not sufficient data; MDD: major depressive disorder; PD: panic disorder; PDSS: panic disorder severity scale; RCT: randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

observe significant differences in adverse events between rTMS and non-rTMS groups separately for GAD and PD studies. The effects of rTMS on symptoms could be optimized by adjusting rTMS parameters for GAD patients.

Similar to PTSD,[15,16] our study suggests that rTMS significantly reduces anxiety and depression symptoms among GAD patients. The effect size of rTMS estimated in our study for anxiety and depression measures among GAD patients was found to be even larger than studies that reported the effect size of CBT for other anxiety disorders,[40] including CBT for GAD[10] and PD.[41] Consistent with our study findings, 1 small meta-analysis[15] and a meta-analysis on predominantly Chinese studies[22] estimated large effect size of rTMS for anxiety scores in GAD patients. Our subgroup analyses by study characteristics indicated that controlled studies, particularly RCTs, produced larger effect sizes of rTMS compared with uncontrolled studies. This attests to the efficacy of rTMS on symptom scores compared with no rTMS in patients with GAD.

Because anxiety symptoms mostly are linked with activation of the right cerebral cortex associated with mood disorders[37,42,43] and rTMS showed a significant reduction in anxiety symptoms in MDD patients, low-frequency rTMS (1 Hz) over the right DLPFC has been used to treat anxiety disorders.[37] Some studies have evaluated the potential use of high-frequency rTMS (≥10 Hz) over the left[32,39] or bilateral[37,38] DLPFC for treating anxiety disorders. We also evaluated rTMS parameters that could be used to optimize treatment efficacy through qualitative and quantitative analyses. In our study, we observed greater improvements in GAD patients who received rTMS over the right DLPFC with low pulse frequency (1 Hz) and low RMT (<100%). However, the greatest improvements in symptoms, particularly for depression symptoms, were observed in a study[34] that used the highest pulse frequency (20 Hz) with the highest number of pulses per session (3,600) over the right DLPFC compared with rest studies. In addition, 1 study[39] showed potential benefit of rTMS only on depression scores using the left DLPFC with 10 Hz pulse frequency and 120% RMT. The high pulse frequency rTMS over the left DLPFC has been suggested for treating MDD.[44] Furthermore, removing 2 bilateral DLPFC studies[37,38] yielding the lowest effect sizes of rTMS substantially reduced heterogeneity across studies in our analysis of GAD studies. This suggests that

		PDSS			
	I^2	N	SMD (95% CI)	*P*	I^2
	79.4%	5	1.19 (-0.02 to 2.40)	.054	86.9%
	0.0%	3[c]	2.25 (1.59 to 2.90)	<.001	0.0%
	NSD	2	-0.07 (-0.58 to 0.45)	.80	0.0%
	79.4%	3	2.25 (1.59 to 2.91)	<.001	0.0%
	85.6%	2	2.23 (1.38 to 3.08)	<.001	0.0%
	NSD	3	0.59 (-0.87 to 2.04)	.43	87.9%
	0.0%	3	0.59 (-0.87 to 2.04)	.43	87.9%
	0.0%	2	2.23 (1.38 to 3.08)	<.001	0.0%
	78.8%	4	1.51 (0.06 to 2.95)	.041	84.7%
	NSD	1	0.08 (-0.51 to 0.67)	.78	NSD

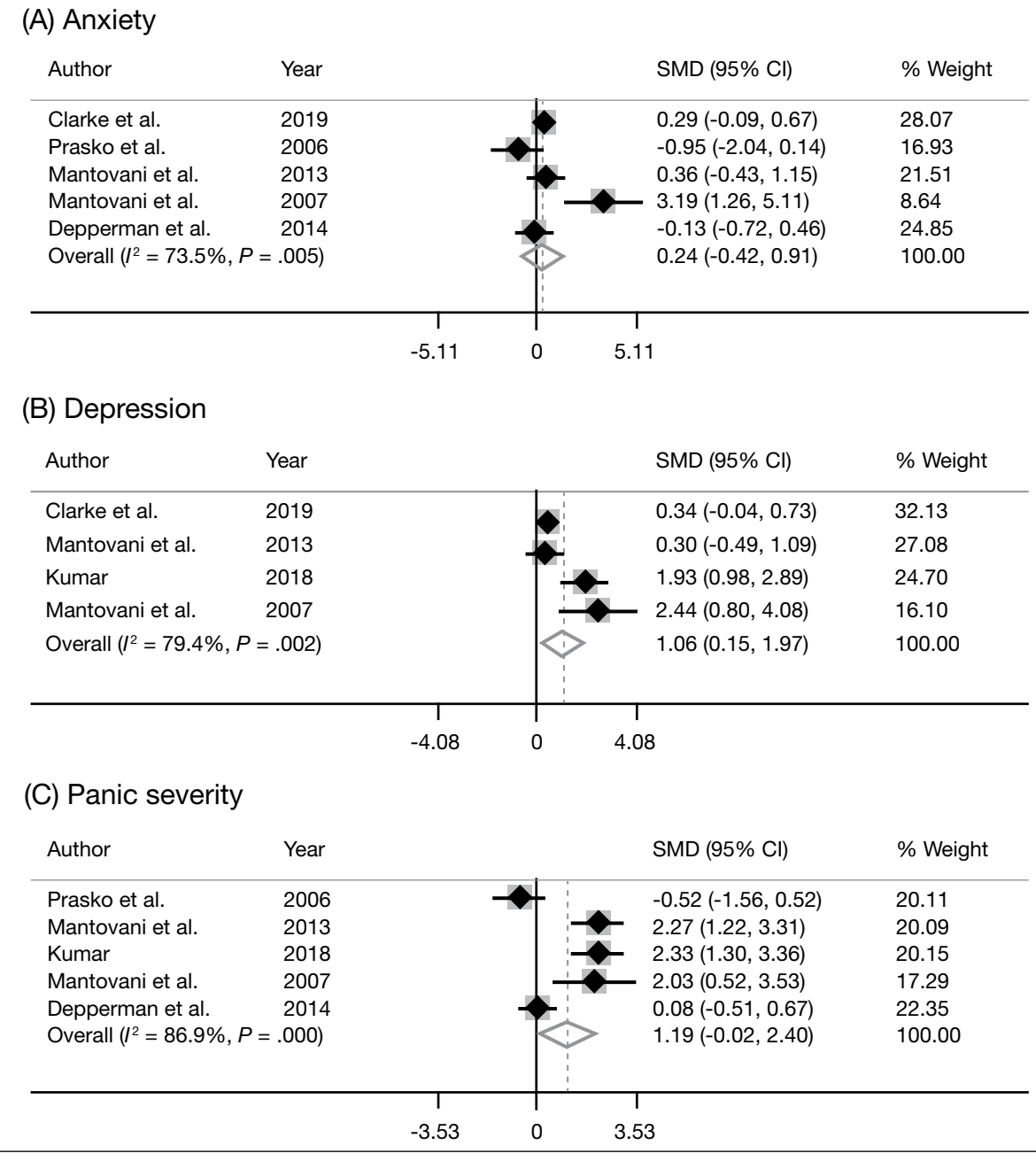
the improvements in symptom scores could be obtained with the less-intensive rTMS parameters (1 Hz pulse frequency, ≤100% RMT) over the right DLPFC with ≥10 sessions. Based on combined qualitative and quantitative analyses, we observed that the effect of rTMS on symptom scores may be optimized by using a pulse frequency of 1 or 20 Hz, RMT of 90% or 110% with >10 sessions with ≥900 pulses per session over the right DLPFC for 6 weeks by targeting GAD patients without comorbidities.

Although rTMS therapy significantly decreased symptom scores among GAD patients, we did not observe improvements in symptom scores after rTMS among PD patients. A previous meta-analysis[15] could not conclude the efficacy of rTMS in PD patients because of the inclusion of only 2 small heterogeneous studies. In our study, rTMS yielded large treatment effects for panic severity and depression symptoms and a moderate effect size with a nonsignificant treatment effect for anxiety symptoms only among patients with PD and comorbid MDD. This suggests that rTMS might be useful in patients with PD and MDD, particularly for alleviating panic severity and depression scores. Three PD studies[29,32,38] did not show any significant improvements in outcome scores after rTMS compared with the non-rTMS group. Of these 3 PD studies, 1 study[38] applied rTMS over the bilateral DLPFC while another study[32] applied 15 sessions of rTMS over the left DLPFC, although the remaining PD studies suggested that rTMS applied other than the right side might not be effective in PD patients. Between 2 RCTs on patients with PD and MDD patients producing no beneficial effects of rTMS, one study[32] applied 15 sessions of rTMS over the left DLPFC at 80% RMT for 3 weeks while the other study[29] applied 10 sessions with 1 Hz frequency, 1,800 pulses per session at 110% RMT over the right DLPFC for 2 weeks. Another RCT[31] that used rTMS parameters similar to the Prasko et al[29] study but applied 20 sessions of rTMS for 4 weeks on patients with PD and MDD produced a significant and sustained treatment effect on panic severity scores without significant improvement in depression scores compared with the non-rTMS group. Another uncontrolled study[36] of patients with PD and MDD produced the largest treatment effect on panic severity and depression scores and applied 20 sessions of rTMS with 20 Hz pulse frequency for 4 weeks. One small study[27] without a parallel control group showed an amplified decrease in all 3 outcome scores by applying 10 sessions of rTMS with 1 Hz pulse frequency at 100% RMT for only 2 weeks. These findings indicate that the low frequency rTMS might be useful in improving symptom scores in patients with PD and MDD. Although we cannot confirm the use of rTMS for treating PD patients because of the heterogeneity in rTMS parameters and limited studies with relatively smaller sample sizes, at ≥20 sessions of rTMS with 1 Hz or 20 Hz frequency at 110% RMT applied for ≥4 weeks might be required to attain improvements in patients with PD and MDD.

Limitations

One of the major limitations of our study is the inclusion of limited studies with small sample sizes with different study designs. However, our analyses did not indicate the presence of a small sample size effect for any outcome measures. We used all the potential study characteristics, including study design, in the heterogeneity assessment analyses and interpreted results accordingly. We presented the overall effect size of rTMS on each outcome score after removing heterogeneity in treatment effects. Although we have used random effects models to obtain pooled estimates, our subgroup analyses might produce biased effect sizes because of large heterogeneity in the subgroup estimates. We performed subgroup analyses

FIGURE 4
Effect of rTMS on anxiety, depression, and panic severity scores in PD patients



PD: panic disorder; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

to optimize treatment effects according to rTMS parameters. Because of the limited number of studies, we could not evaluate the effect of rTMS on outcome scores according to patients with GAD and MDD, bilateral or left DLPFC studies in PD, and RCT studies involving only patients with PD and MDD. Although our meta-analysis could not examine the effects of rTMS according to joint rTMS parameters, our qualitative analysis determined the potential effects of combined rTMS parameters on various outcomes separately for GAD and PD studies. In view of the limited sample size in subgroup analyses with complex interaction in comorbidities and rTMS

parameters, the results of subgroup analyses should be interpreted cautiously. Despite these limitations, our study is the most comprehensive systematic review and meta-analysis in GAD and PD patients that included homogenous measures of symptoms and reported the effect of rTMS on symptom scores in GAD and PD patients with or without psychiatric comorbidities separately according to rTMS parameters. The qualitative analyses in the study reported the combined effects of multiple rTMS parameters on symptom scores.

CONCLUSIONS

Our study confirms the therapeutic potential and safety of rTMS in GAD patients but not in PD patients. Our study also suggests that rTMS is an effective treatment option for patients with GAD with or without comorbidities. Low-frequency rTMS (1 Hz) with ≥90% RMT over the right DLPFC with a high number of sessions (>10) for a long treatment duration (>3 weeks) may optimize the effect of rTMS in GAD patients. rTMS demonstrated a positive treatment effect particularly in PD with MDD patients, but not for all PD patients. Future randomized studies are required to confirm the efficacy of rTMS among patients with PD and MDD. ■

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SUPPLEMENTAL TABLE 1

Adverse events in rTMS and control groups

Study	Headache	Pain at stimulation site or scalp pain or discomfort	Neck pain	Facial twitch	Dizziness or lightheaded	Seizure	Pin prick sensation
Huang et al[35] (2018)	Active group = 5/18; sham group = 3/18		Active group = 6/18; sham group = 4/18				
Lu et al[37] (2018)							
Dilvok et al[34] (2017)				Active group = 15/15; sham group = 25/25	Active + sham group = 3/40	Active group = 1/15	
Diefenbach et al[33] (2016)	Active group = 6/13; sham group = 3/12	Active group = 11/13; sham group = 8/12		Active group = 6/13	Sham group = 2/12		Active group = 9/13; sham group = 10/12
Bystritsky et al[30] (2008)							
Zhang et al[39] (2019)	Active group = 3/117						
Clarke et al[38] (2019)							
Clarke et al[38] (2019)							
Prasko et al[29] (2007)							
Mantovani et al[31] (2013)	Phase 1: active group = pre 12.8% and post 15.5% of 12; sham group = pre 19.5% and post 22.5% of 13; Phase 2: active group = pre 17.1% and post 18.2% of 12	Phase 1: active group = pre 1% and post 9.5% of 12; sham group = pre 2.6% and post 11.8% of 13; Phase 2: active group = pre 1.2% and post 10.9% of 12	Phase 1: active group = pre 11% and post 15% of 12; sham group = pre 14.8% and post 17.4% of 13; Phase 2: active group = 12.9% and post 16.6% of 12				
Kumar et al[36] (2018)	Active group = 1/13	Active group = 2/13					
Mantovani et al[27] (2007)	Active group = 5/18; sham group = 3/18		Active group = 6/18; sham group = 4/18				
Depperman et al[32] (2014)							
White et al[28] (2015)							

rTMS: repetitive transcranial magnetic stimulation.

Adverse events							
Facial pain (including eye pain)	**Toothache**	**Musculoskeletal discomfort**	**Scalp burns**	**Hearing impairment**	**Impaired cognition**	**Trouble concentrating**	**Memory impairment**
Active group = 3/13; sham group = 1/12	Active group = 3/13						
		Active group = 2/117					
			Phase 2: active group = post 0.3% of 12	Phase 1: sham group = pre 1.5% and post 0.5% of 13; Phase 2: active group = post 0.3% of 12	Phase 1: active group = pre 3% and post 6% of 12; sham group = pre 4.5% and post 4% of 13; Phase 2: active group = pre 0.9% and post 1.2% of 12	Phase 1: active group = pre 13.5% and post 12% of 12; sham group = pre 12.1% and post 10% of 13; Phase 2: active group = pre 4.9% and post 3.4% of 12	Phase 1: active group = pre 6% and post 4.5% of 12; sham group = pre 6% and post 5.5% of 13; Phase 2: active group = pre 1.4% and post 0.9% of 12

SUPPLEMENTAL TABLE 2

Comparisons of study characteristics and rTMS parameters between types of anxiety disorders (GAD vs PD)

Criteria	GAD	PD	*P*
	Mean (SD); median	**Mean (SD), median**	
Age (active group)	43.6 (4.5); 44.9	40.1 (6.4); 43.8	.282
Female	0.57 (0.10); 0.58	0.60 (0.09); 0.61	.671
rTMS parameters			
Frequency (Hz)	6.28 (7.39); 1	6.6 (8.4); 1	1.00
Motor threshold	98.6 (14.6); 90	103.3 (12.1), 110	.540
Number of sessions	15.2 (9.8); 10	15 (5); 15	.701
Treatment duration (d)	23.8 (14.5); 17.5	21 (7); 21	.925
	Frequency (%)	**Frequency (%)**	
Stimulation site			
Right DLPFC	4 (57.1%)	3 (60%)	1.00
Left DLPFC	1 (14.3%)	1 (20%)	
Bilateral	2 (28.6%)	1 (20%)	
Comorbidities			
Absent	4 (57.1%)	2 (33.3%)	.592
Present	3 (42.9%)	4 (66.7%)	
Study size			
Small	3 (42.9%)	4 (66.7%)	.592
Large	4 (57.1%)	2 (33.3%)	
Frequency (Hz)			
Low	4 (57.1%)	3 (60%)	1.00
High	3 (43.9%)	2 (40%)	
Motor threshold			
Low	4 (57.1%)	2 (33.3%)	.592
High	3 (42.9%)	4 (66.7%)	
Number of sessions			
Low	4 (66.7%)	2 (40%)	.567
High	2 (33.3%)	3 (60%)	

DLPFC: dorsolateral prefrontal cortex; GAD: generalized anxiety disorder; PD: panic disorder; rTMS: repetitive transcranial magnetic stimulation.

SUPPLEMENTAL TABLE 3

Quality assessment of studies included in the systematic review

Study	Study type	Methodological items for nonrandomized studies				
		A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint
Huang et al[35] (2018)	RCT	2	1	2	2	2
Lu et al[37] (2018)	Noncomparative	2	1	2	2	2
Dilvok et al[34] (2017)	RCT	2	1	2	2	2
Diefenbach et al[33] (2016)	RCT	2	1	2	2	2
Bystritsky et al[30] (2008)	Noncomparative	2	1	2	2	2
Zhang et al[39] (2019)	Noncomparative	2	1	2	2	2
Clarke et al[38] (2019)	Comparative	2	2	2	2	2
Prasko et al[29] (2007)	RCT	2	1	2	2	2
Mantovani et al[31] (2013)	RCT	2	1	2	2	2
Kumar et al[36] (2018)	Noncomparative	2	2	1	2	2
Mantovani et al[27] (2007)	Noncomparative	2	1	2	2	2
Depperman et al[32] (2014)	RCT	2	1	2	2	2
White et al[28] (2015)	Noncomparative	2	1	2	2	2

RCT: randomized controlled trial.

			Additional criteria in the case of comparative study				
Follow-up period appropriate to the aim of the study	**Loss to follow up <5%**	**Prospective calculation of the study size**	**An adequate control group**	**Contemporary groups**	**Baseline equivalence of groups**	**Adequate statistical analyses**	**Total**
2	2	0	2	2	2	1	20
2	2	0	0	0	0	0	13
2	1	0	2	2	2	1	19
2	2	0	2	2	2	2	21
2	2	0	0	0	0	0	13
2	1	0	0	0	0	0	12
2	1	1	0	2	2	1	19
2	2	0	2	2	2	1	20
2	1	0	2	2	2	1	19
2	2	0	0	0	0	0	13
2	2	0	0	0	0	0	13
2	2	2	2	2	2	1	22
2	2	0	0	0	0	0	13

SUPPLEMENTAL TABLE 4

Assessment of publication bias using Egger's test

Bias for parameters	Study	N	Beta coefficient	Standard error	*P*
Anxiety	GAD	7	2.81	2.18	.255
Depression	GAD	6	2.88	3.13	.410
Anxiety	PD	5	0.95	2.12	.684
Depression	PD	4	3.28	1.63	.582
Panic severity	PD	5	4.82	3.68	.282

GAD: generalized anxiety disorder; PD: panic disorder.

SUPPLEMENTAL TABLE 5

The effect of rTMS on outcome scores by rTMS parameters among GAD patients

	Anxiety				Depression			
rTMS parameters	**N**	**SMD (95% CI)**	***P***	***I*²**	**N**	**SMD (95% CI)**	***P***	***I*²**
Frequency								
<10 Hz	4	1.8 (1.39 to 2.21)	<.001	0.00%	3	1.23 (0.75 to 1.71)	<.001	0.00%
≥10 Hz	3	1.04 (0.12 to 1.95)	.026	94.20%	3	2.05 (0.61 to 3.5)	.005	97.20%
Motor threshold								
≤100	4	1.8 (1.39 to 2.21)	<.001	0.00%	3	1.23 (0.75 to 1.71)	<.001	0.00%
>100	3	1.04 (0.12 to 1.95)	.026	94.20%	3	2.05 (0.61 to 3.5)	.005	97.20%
Number of sessions								
≤10	4	1.66 (1.41 to 1.9)	<.001	0.00%	3	1.48 (0.92 to 2.05)	<.001	58.30%
>10	2	1.34 (0.79 to 1.89)	<.001	0.00%	2	2.9 (0.05 to 5.75)	.046	93.10%
Treatment duration								
≤3 weeks	3	1.89 (1.43 to 2.35)	<.001	0.00%	2	1.13 (0.56 to 1.7)	<.001	0.00%
>3 weeks	4	1.12 (0.35 to 1.9)	.004	91.60%	4	1.9 (0.73 to 3.08)	.002	95.80%
Stimulation site								
Right DLPFC	4	1.69 (1.21 to 2.16)	<.001	16.00%	4	2.01 (0.7 to 3.31)	.003	87.40%
Left DLPFC	1	1.56 (1.27 to 1.85)	<.001	NSD	1	1.82 (1.51 to 2.12)	<.001	NSD
Bilateral	2	0.96 (-0.36 to 2.28)	.15	93.30%	1	0.39 (0.1 to 0.69)	.01	NSD

DLPFC: dorsolateral prefrontal cortex; GAD: generalized anxiety disorder; NSD: not sufficient data; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

SUPPLEMENTAL TABLE 6

The effect of rTMS on outcome scores by rTMS parameters in PD patients

	Anxiety				Depression		
rTMS parameters	**N**	**SMD (95% CI)**	***P***	***I²***	**N**	**SMD (95% CI)**	***P***
Frequency							
<10 Hz	3	0.68 (–1.11 to 2.46)	.457	85.40%	2	1.24 (–0.84 to 3.33)	.243
≥10 Hz	1	0.29 (–0.09 to 0.67)	.136	NSD	2	1.08 (–0.48 to 2.63)	.175
Motor threshold							
≤100	2	1.4 (–1.84 to 4.64)	.398	90.40%	1	2.44 (0.8 to 4.08)	.004
>100	3	0.05 (–0.58 to 0.68)	.885	56.80%	3	0.78 (–0.09 to 1.65)	.08
Number of sessions							
≤10	2	1.04 (–3.01 to 5.09)	.615	92.60%	1	2.44 (0.8 to 4.08)	.004
>10	2	0.05 (–0.43 to 0.52)	.851	0.00%	2	1.09 (–0.51 to 2.7)	.182
Treatment duration							
≤3 weeks	3	0.46 (–1.2 to 2.12)	.586	85.20%	1	2.44 (0.8 to 4.08)	.004
>3 weeks	2	0.3 (–0.04 to 0.65)	.084	0.00%	3	0.78 (–0.09 to 1.65)	.08
Stimulation site							
Right DLPFC	3	0.68 (–1.11 to 2.46)	.457	85.40%	2	1.24 (–0.84 to 3.33)	.243
Left DLPFC	1	-0.13 (–0.72 to 0.46)	.67	NSD	NSD	NSD	NSD
Bilateral	1	0.29 (–0.09 to 0.67)	.136	NSD	1	0.34 (–0.04 to 0.73)	.078

DLPFC: dorsolateral prefrontal cortex; NSD: not sufficient data; PD: panic disorder; PDSS: panic disorder severity scale; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference.

	PDSS			
I^2	N	SMD (95% CI)	*P*	I^2
81.2%	3	1.23 (–0.67 to 3.13)	.204	87.2%
89.1%	1	2.33 (1.3 to 3.36)	<.001	NSD
NSD	2	0.93 (–0.96 to 2.82)	.336	82.0%
79.0%	3	1.36 (–0.48 to 3.2)	.148	89.4%
NSD	2	0.69 (–1.8 to 3.19)	.587	86.6%
85.1%	3	1.52 (–0.14 to 3.16)	.072	90.6%
NSD	3	0.38 (–0.75 to 1.51)	.514	73.9%
79.0%	2	2.3 (1.57 to 3.03)	<.001	0.0%
81.2%	3	1.23 (–0.67 to 3.13)	.204	87.2%
NSD	1	0.08 (–0.51 to 0.67)	.783	NSD
NSD	NSD	NSD	NSD	NSD